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HYPERTROPHY OF MUSCLE IN SUPRARENAL VEIN IN HYPERTENSION

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The veins of the suprarenal glands are known for their well developed musculature. The amount of smooth muscle elements in these veins is so considerable that it is equal to that of some of the medium sized arteries. It has been noticed, furthermore, that the distribution of the muscle bundles in the vessel wall is irregular, as some of the bundles are eccentrically placed, particularly about the opening of those smaller veins which open into the larger vessels in the central portion of the suprarenal gland (Ferguson,[1] Dubreuil,[2] Pendelaire,[3] Maresch [4] and Materna).

Several hypotheses have been made to explain the significance of this musculature, and it has been suggested that the particularly powerful longitudinal muscle bundles may be instrumental in pressing out the secretum of the gland in response to nervous stimulation. It has also been suggested that the lumen of the smaller veins may temporarily be obstructed if the muscle bundles about their orifice contract. This would avert the stream of the discharge back to the collaterals which connect the suprarenal circulation directly with the liver and kidney circulation respectively.

In a study of the development of this peculiar musculature of the various ages, the following conclusions are reached: In the fetus and the new-born child this musculature cannot be seen; in a later stage, it gradually develops, and only in the adult, is its full development seen. In adults, however, the amount of musculature varies considerably, and one of us who has studied the morphology of the suprarenal glands during the last twenty years has noticed that the mass of the musculature varies according to the state and condition of the circulatory organs. To bear

1. Ferguson: Am. J. Anat. **5**:63, 1906.
2. Dubreuil: Compt. rend. Soc. de biol. **83**:1096, 1920.
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4. Maresch: Wien. klin. Wchnschr. **1**:44, 1921.

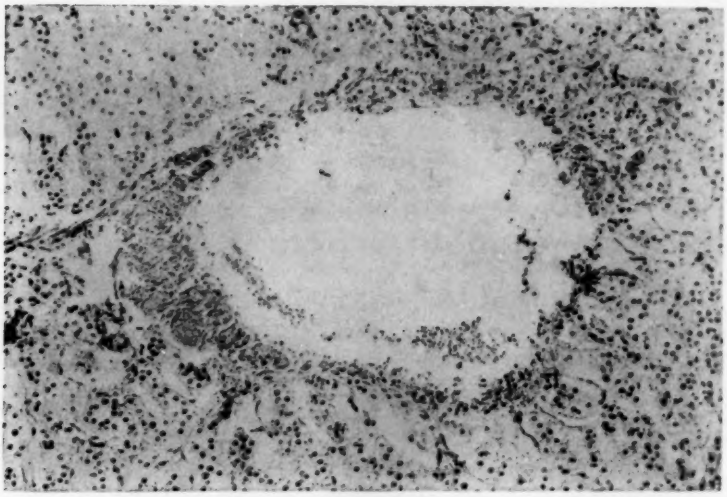

Fig. 1.—Normal large suprarenal vein with eccentric arrangement of longitudinal muscle bundles. Magnification: Leitz apochromate 16 mm.; periplane eye piece no. 4.

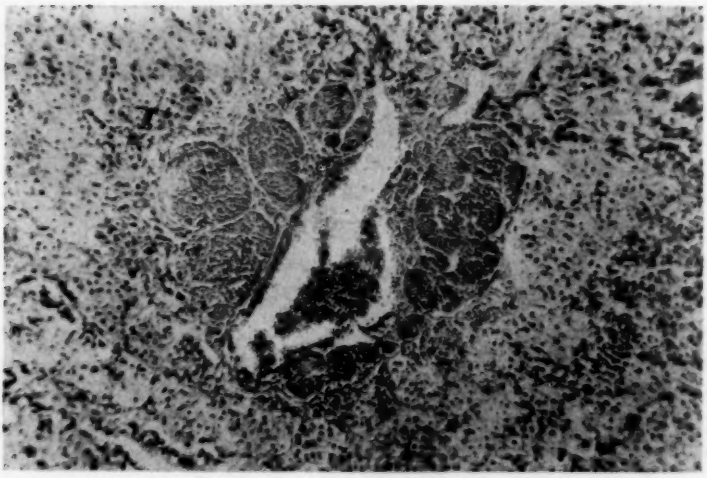

Fig. 2.—Hypertension: suprarenal vein with hypertrophic musculature. Magnification: Leitz apochromate 16 mm.; periplane eye piece no. 4.

out this observation, we have measured the thickness of the musculature in a series of fifty-one cases taken at random from our autopsy material. In order to obtain a fair comparison, we have used the suprarenal glands of adults only; furthermore, we measured always the left gland, and made our sections consistently of identical parts of the organs. We cut the left suprarenal gland in three places, dividing it into four almost

TABLE 1.—*Cases of Hypertension*

Case	Age	Sex	Blood Pressure	Anatomic Conditions	Suprarenal Musculature
1	67	F	230/115	Heart: normal Vessels: general arteriosclerosis Kidneys: pyelonephritis	++
2	59	M	224/100	Heart: enlarged musculature throughout Vessels: generalized arteriosclerosis Kidneys: granular	+++
3	27	F	190/134	Heart: normal Vessels: arteriosclerosis Kidneys: granular, contracted	++
4	46	M	190/134	Heart: enormous dilated right ventricle with hypertrophy of right and left ventricle Kidneys: small granular, atrophied	+++
5	45	F	230/120	Heart: enlarged and hypertrophied throughout Vessels: arteriosclerosis, especially of coronaries Kidneys: granular	+++
6	74	M	180/ 64	Heart: hypertrophied left ventricle..... Vessels: arteriosclerosis Kidneys: arteriosclerotic	++
7	55	F	215/ ?	Heart: enlarged throughout; hypertrophy of left ventricle Vessels: generalized arteriosclerosis Kidneys: arteriosclerotic and thrombotic contraction of left kidney	++
8	25	F	200/ ?	Heart: normal Vessels: normal Kidneys: subacute glomerulo nephritis	++
9	67	F	170/ 90	Heart: hypertrophy of left ventricle..... Vessels: arteriosclerosis Kidneys: normal	++
10	65	F	160/120	Heart: hypertrophy of left ventricle..... Vessels: arteriosclerosis Kidneys: normal	++
11	53	M	180/102	Heart: hypertrophy of left ventricle..... Vessels: generalized arteriosclerosis Kidneys: atrophy of right kidney	++
12	40	M	160/ 80	Heart: hypertrophy of left ventricle..... Vessels: normal Kidneys: normal	++
13	59	F	183/116	Heart: hypertrophy of left ventricle..... Vessels: generalized arteriosclerosis Kidneys: granular, contracted	++

equal parts, and examined histologically sections from the three lower parts, leaving only the top portion unexamined. An equal number of vessels were measured in all the cases, and care was taken that the vessels of approximately equal size only should be compared.

We divided our material into three groups, according to the clinical and anatomic observations. The first group consists of cases of manifest hypertension only. Table 1 shows that in these cases a hypertrophy of

the left side of the heart was invariably present, as were also changes of the kidneys and the arterial system.

The second group consists of those cases in which during hospital observation preceding death either hypertension was not noted, or data concerning the blood pressure were not available. The anatomic observations, however, in all these cases indicated that there were severe

TABLE 2.—*Cases with Arteriosclerosis and Chronic Renal Changes*

Case	Age	Sex	Blood Pressure	Anatomic Conditions	Laboratory Results	Suprarenal Musculature
1	49	M	120/80	Heart: coronary thrombosis Vessels: arteriosclerosis Kidneys: granular	Urine: specific gravity, 1.014; albumin, trace; few red blood cells	+
2	45	M	140/90	Heart: normal..... Vessels: normal Kidneys: glomerulo nephritis	Urine: specific gravity, 1.007; albumin, 2 plus; hyaline and granular casts	++
3	42	F	95/50	Heart: normal..... Vessels: arteriosclerosis Kidneys: arteriosclerotic	Urine: specific gravity, 1.014; albumin, trace; many granular casts Blood chemistry: creatinine, 1.6; urea nitrogen, 12; uric acid, 4.4	+
4	40	M	118/60	Heart: normal..... Vessels: arteriosclerosis Kidneys: arteriosclerotic	Urine: specific gravity, 1.020; albumin, 1 plus; granular casts	+
5	60	M	130/80	Heart: apical aneurysm of left ventricle Vessels: generalized arteriosclerosis Kidneys: normal	.....	++
6	35	M	120/70	Heart: enlarged and hypertrophied throughout Vessels: normal Kidneys: pyelonephritis	Blood chemistry: creatinine, 3; urea nitrogen, 56.6	++
7	38	M	100/70	Heart: hypertrophy of left ventricle Vessels: arteriosclerosis Kidneys: normal	.....	++
8	45	M	130/70	Heart: normal..... Vessels: normal Kidneys: glomerulo nephritis	Urine: specific gravity, 1.013; albumin, 3 plus; hyaline and granular casts Blood chemistry: urea nitrogen, 84; creatinine, 5.5	++
9	40	M	120/60	Heart: hypertrophy of left ventricle Vessels: syphilitic aortitis; generalized arteriosclerosis	.....	++
10	60	M	120/80	Heart: normal..... Vessels: arteriosclerosis	.....	++
11	50	M	120/65	Heart: normal..... Vessels: normal Kidney: chronic nephritis	Urine: specific gravity, 1.016; albumin, 4 plus; many granular casts	++

disturbances of the vascular apparatus, such as advanced arteriosclerosis and chronic changes of the kidneys. Finally, in some of these cases, laboratory observations such as the blood chemistry or urinanalysis indicated the presence of disturbances which are usually concomitant with hypertension.

It is of importance that in the great majority of these cases, the patient was admitted to the hospital with an acute infectious process which terminated fatally shortly afterward. The anatomic diagnosis was pneumonia, urogenital sepsis or similar condition. It is reasonable that

the blood pressure of a patient with such a condition will not give a fair indication of its level prior to the onset of the fatal infectious process. In the other few cases of this group in which an infectious process was not present, the proper function of the heart was interfered with by thrombosis of the coronary arteries, fibrinous myocarditis or the formation of an apical aneurysm.

The last group eventually consisted of all the cases without either clinical or anatomic evidence as to the prevalence of hypertension or renovascular alterations.

In the tables, the increased musculature is indicated by + signs, according to the degree of hypertrophy. The following measurements were used to denote the + signs.

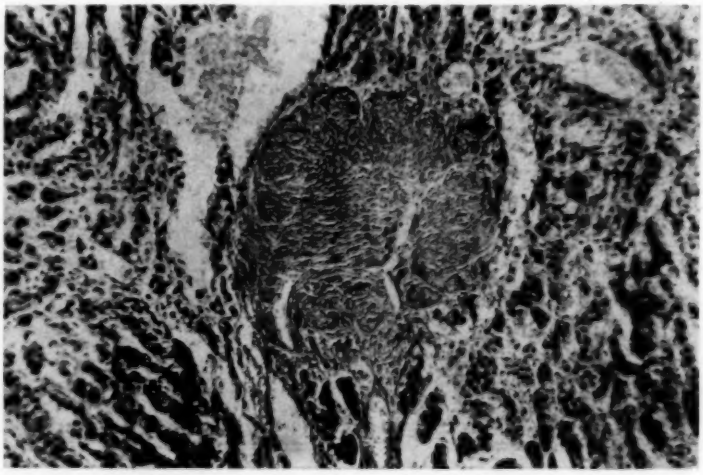

Fig. 3.—Hypertension: smaller vein than that in figure 2, with excessive muscular hypertrophy; lumen almost obstructed. Magnification: Leitz apochromate 16 mm.; periplane eye piece no. 4.

$\frac{1}{23}$ to $\frac{1}{13}$ = +
$\frac{1}{13}$ to $\frac{1}{7}$ = ++
$\frac{1}{7}$ to $\frac{1}{3}$ = +++

In order to determine as accurately as possible whether hypertrophy was present, we used the following system: In each case, nine veins of various sizes were measured. The size of the vessel was expressed by a figure obtained by multiplying its two largest diameters. The measurements of the nine vessels were compared to the thickness of their musculature. Thus, a quotient was obtained which in the normal cases varied from 1:23 to 1:60, giving the average quotient of 1:36 in normal cases. In cases of hypertension, the quotient varied from 1:3 to 1:13, with an average of 1:9. Hence, the musculature of the suprarenal veins in

TABLE 3.—*Cases Without Hypertension*

Case	Age	Sex	Blood Pressure	Anatomic Conditions of Heart, Kidneys and Vessels	Diagnosis	Musculature
1	23	M	110/70	Normal	Sarcoma of the femur	—
2	38	M	88/72	Normal	Miliary tuberculosis and tuberculosis of brain	—
3	59	M	105/90	Normal	Tumor of hypophysis	++
4	24	F	120/70	Normal	Streptococcus meningitis	—
5	50	M	142/70	Heart and kidneys normal; vessels somewhat thickened	Cerebral injury with hemiplegia	—
6	68	M	152/90	Normal	Streptococcus meningitis	—
7	54	M	133/86	Normal	Carcinoma of hepatic duct	+
8	30	F	106/45	Normal	Hemorrhage into abdominal cavity: fibrinous peritonitis	—
9	30	F	105/60	Normal	Bronchopneumonia, myasthenia gravis	—
10	70	F	110/60	Normal	Carcinomatous ulcer of duodenum	—
11	48	F	130/80	Normal	Carcinoma of ovary and thrombosis of femoral vein	—
12	28	F	125/70	Normal	Sarcoma of duodenum	+
13	19	F	90/60	Heart four times normal in size; vessels and kidneys normal	Mitral stenosis, infarct of lung	—
14	50	F	130/70	Normal	Bronchopneumonia	—
15	47	F	.....	Normal	Asthma; dilatation of heart	—
16	23	F	120/60	Normal	Postabortal sepsis	—
17	40	M	100/60	Heart and vessels normal; kidneys, tuberculosis	Tuberculosis of left kidney, perinephritis	—
18	48	M	130/70	Normal	Tabes, syphilitic aortitis, aneurysm of aorta	—
19	40	M	110/70	Normal	Carcinoma of the stomach	—
20	44	M	120/70	Normal	Cerebral spinal meningitis	—
21	14½	F	82/60	Normal	Septicemia	—
22	45	M	140/80	Normal	Bronchopneumonia	—
23	43	M	.....	Normal	Pulmonary abscess	—
24	23	F	.....	Heart: increase in musculature of right side, decrease in left ventricle	Emboli of right internal carotid and middle cerebral artery	—
25	80	F	.....	Normal	Hypertrophied prostate	—
26	55	F	.....	Normal	Lung abscess and pyemia	—
27	25	F	.....	Normal	Puerperal sepsis	—

TABLE 4.—*Thickness of Wall of Central Veins of Suprarenal in Hypertension and Normally*

Hypertension		Normal	
Case 1, table 1		Case 5, table 3	
Lumen, 15.4 × 4.4 microns	Musculature, 3.1 microns	Lumen, 14 × 3 microns	Musculature, 1.5 microns
Case 2, table 1		Case 13, table 3	
Lumen, 12.3 × 5 microns	Musculature, 6.1 microns	Lumen, 11.5 × 4.2 microns	Musculature, 0.37 microns
Case 3, table 1		Case 9, table 3	
Lumen, 10.7 × 5 microns	Musculature, 3.3 microns	Lumen, 10.7 × 3 microns	Musculature, 0.77 microns
Case 7, table 1		Case 8, table 3	
Lumen, 24.6 × 2 3 microns	Musculature, 5 microns	Lumen, 20 × 4.6 microns	Musculature, 0.77 microns
Case 4, table 1		Case 18, table 3	
Lumen, 12.3 × 6.3 microns	Musculature, 3.7 microns	Lumen, 12.3 × 2.7 microns	Musculature, 0.77 microns
Case 5, table 2		Case 12, table 3	
Lumen, 10.7 × 6.9 microns	Musculature, 5.7 microns	Lumen, 13.7 × 3 microns	Musculature, 2.3 microns
Case 6, table 1		Case 1, table 3	
Lumen, 10.3 × 2.7 microns	Musculature, 3.9 microns	Lumen, 7.7 × 0.77 microns	Musculature, 0.37 microns
Case 9, table 1		Case 26, table 3	
Lumen, 10.3 × 2 microns	Musculature, 3.3 microns	Lumen, 12.3 × 4.2 microns	Musculature, 0.77 microns

patients with hypertension compares to that of the suprarenal veins in normal persons as 4:1. The cases reported in our table 2 did not differ essentially from those collected in table 1, both groups showing approximately the same amount of hypertrophy.

We have also attempted to measure the thickness of the muscular wall of the central veins of the suprarenal glands. Table 4 demonstrates the figures obtained in eight cases of hypertension and a similar number of normal cases.

As seen in table 4, the thickness of the muscle wall of the central vein in normal persons varies between 0.4 and 2.33 microns, and the average is 1.1 microns. In cases of hypertension, the thickness of the musculature varies between 3 and 6.1 microns, and the average is 4.2 microns. The relation between the average quotients of the two types of central veins is almost the same as that between the average quotients of the smaller veins. The sizes of the vessels compared were approximately equal.

In our third group, which we are using as a comparison to our first two groups, the subjects were of various ages. Some of them were old; nevertheless, their venous musculature did not show an increase, showing that such an increase in size is not due merely to advancing age. There were only three cases in the latter group in which the patient, although exempt from renovascular disease and without clinical symptoms of hypertension, nevertheless revealed an increased musculature of the suprarenal veins. In two of the cases the increases were rather slight, while in one case the musculature was bulky and almost comparable to that in some cases of hypertension. It is peculiar that in all three cases concerned malignant tumors were present. The two cases in which there was slight muscular hypertrophy were both instances of malignancy of the upper part of the abdomen: one was a case of carcinoma of the bile duct, with massive fibrous adhesions in the retroperitoneal tissue embedding both suprarenal glands, while the other was a case of pancreatic tumor, also with involvement of the retroperitoneal lymph nodes. Without undue emphasis, the possibility is suggested that in these two cases the discharge of the suprarenal venous blood may have encountered mechanical obstacles which might have been responsible for the muscular hypertrophy. In the third case such anatomic impairment of the suprarenal circulation was not observed. In this case, however, a malignant endothelioma of the dura mater was situated on the basis of the skull and invaded the sella turcica. The posterior lobe of the hypophysis was completely destroyed, while the anterior lobe, although flattened and compressed, was fairly well maintained. As our other cases did not show a musculature comparable to that in this case in which the posterior pituitary lobe was incapacitated, it may be that an increased suprarenal function was attempting to substitute for the loss of its synergist, the posterior pituitary lobe.

We have attempted to demonstrate the effect of the hypertrophied musculature described on the circulation within the suprarenal gland and, consecutively, on its function by means of another method. While the left suprarenal gland was used for histologic examinations, methylene blue gelatin mass was injected through the central vein of the right one, in order to determine by injection of the same amount under the same pressure whether there was any difference in the distribution of the dye. After dehydration, the specimen was cleared with oil of wintergreen. At first too large a quantity of dye was injected, and an even distribution was obtained throughout the whole organ, regardless of the structure of the vessel. The amount of dye was gradually decreased, until finally

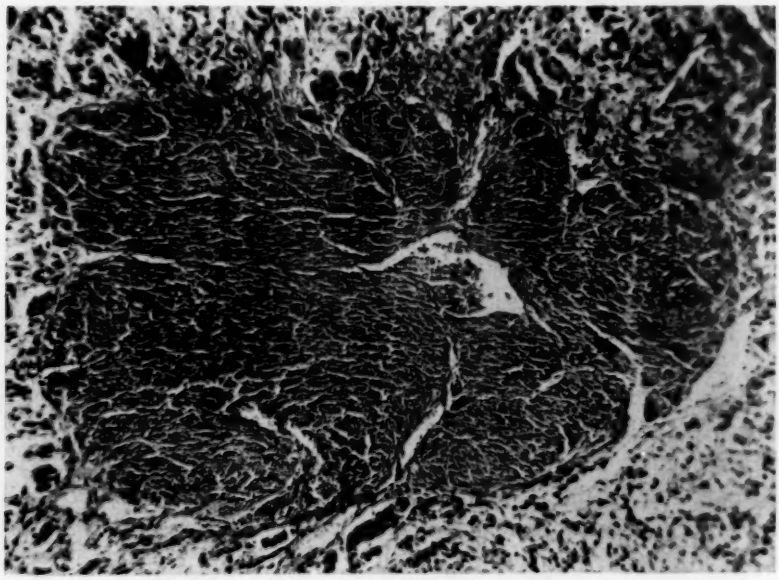

Fig. 4.—Hypertension: larger suprarenal vein considerably narrowed by excessive muscular hypertrophy. Magnification: Leitz apochromate 16 mm.; periplane eye piece no. 4.

0.25 cc. was injected into each gland. In the latter series, which comprised five patients with hypertension and hypertrophied musculature in whom the injections were successful and five normal patients, we observed a striking difference in the distribution of the dye. In the normal patients, the dye filled out the vessels evenly throughout the whole organ. In the patients with hypertension, the bulk of the dye was retained in the central portion and reached the periphery only in irregular processes. In between the latter, extensive areas remained uninjected. We do not hesitate to explain these observations by the different structure of the musculature. It has been mentioned previously that the

venous musculature, if hypertrophied, seems to block many of the small vessels which drain the blood from the cortex. Undoubtedly unusual force must be applied to clear the passage and to inject the areas concerned.

It is generally accepted that muscular hypertrophy of a hollow organ is brought about by continuous overexertion of its muscular elements right above the place where the passage becomes obstructed. Such hypertrophy is commonly seen in the gastro-intestinal canal above strictures; in the left side of the heart in patients with valvular lesions, or in the right side of the heart in obstructions of the pulmonary circulation. A similar result is obtained if continuous or often repeated exertion is induced by nervous stimulation. At any rate, muscular hypertrophy expresses increased muscular function, and it is but fair to assume that hypertrophy of the musculature in the suprarenal veins also expresses an accommodation to a constant strain to which the vessel wall has been subjected.

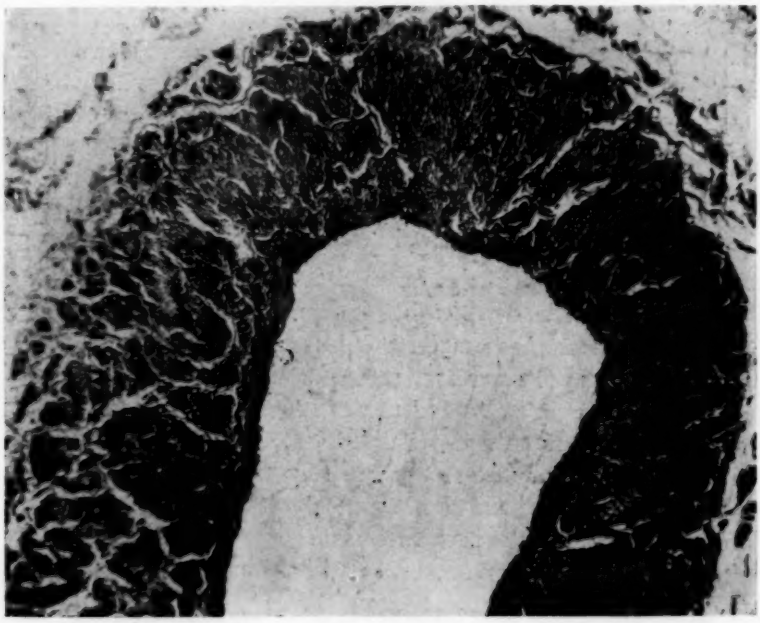

Fig. 5.—Vena centralis of normal suprarenal gland of middle aged man. Magnification: Leitz apochromate 16 mm.; periplane eye piece no. 4.

The suprarenal vein is looked on as the excretory duct of the glandular organ. The presence of strong muscle bundles in the wall, and particularly about the orifice of the smaller venules which lead into the centrally located larger sinus-like spaces, suggests a relationship of

these muscle bundles to the regulation of the glandular discharge. The fact that the blood collected by the small cortical capillaries empties through small veins in those larger sinuses is accepted. It is within reason that the active substance, discharged from the cortical cells, will reach the sinuses on the way described, and will mix therein with the discharge of the medullary cells. The central vein, after collecting the whole output of the glandular organ, liberates its blood into the vena cava. It is questionable, however, whether the mixture of this blood is invariable, or, in other words, if the blood of the suprarenal vein contains always an identical concentration of both epinephrine and

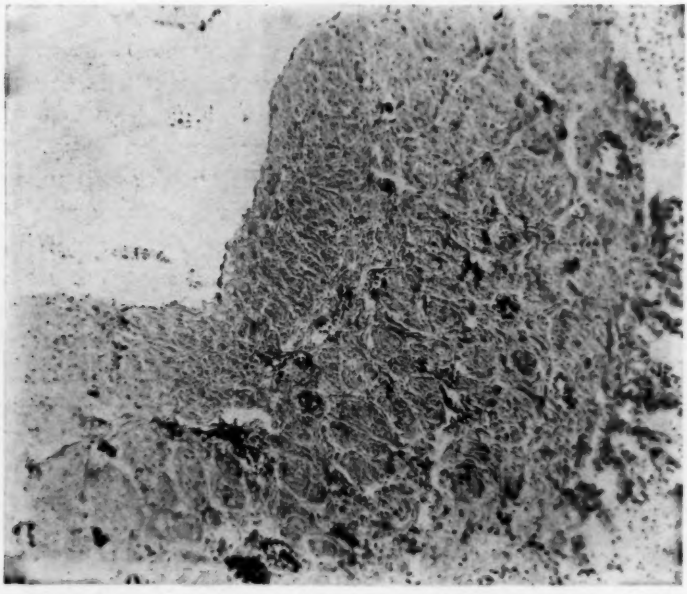

Fig. 6.—Hypertension: vena centralis, showing marked hypertrophy of the muscle. Magnification: Leitz apochromate 16 mm.; periplane eye piece no. 4.

cortical products. To assume that contractions or relaxations of the intraglandular venous musculature regulate the composition of the suprarenal discharge, either by retaining temporarily a part of the glandular output or by admitting the same more freely, is suggestive. The composition of the glandular discharge might be influenced also by deviation of its parts through the channels known as collaterals which drain to the kidney and liver circulation.

Further investigations are needed to unveil the exact mechanism of suprarenal secretion as regulated by its muscular excretory system. So far, one thing only can be stated definitely: that in hypertension, the musculature of the suprarenal veins is hypertrophic. It seems reasonable

to assume that such hypertrophy is the result of constant overexertion resulting from the attempt to regulate and hold back the excessive liberation of the pressor glandular discharge.

Similar hypertrophy has been observed also in a series of cases of which we could not get direct evidence to prove that hypertension prevaled at least in a period prior to that of the last hospital confinement. All the cases, however, had one point in common: advanced impairment of the arteries, with more or less severe involvement of the kidneys. Further discussion of the question whether the terminal infectious process or the lesions of the heart muscle account for the subsidence of the increased blood pressure or whether the blood pressure was not

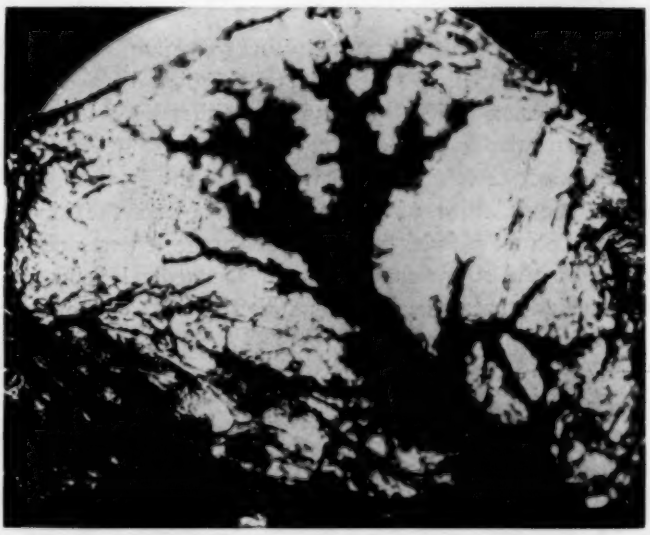

Fig. 7.—Hypertension: injection through the central vein with methylene blue gelatin, cleared with wintergreen oil. The abrupt ending of the injection in the veins should be noted. Magnification: Leitz summar 64 mm.

increased even in an earlier period is futile, although the injured arteries would indicate that there were such circulatory disturbances. We are of the opinion that the cases in question were actually such cases of hypertension, masked by intercurrent diseases. As this is yet a matter of contention, we choose to maintain the separation of our material into three groups: manifest hypertension with hypertrophic musculature, renovascular alterations without manifest hypertension and with hypertrophic musculature and musculature of normal size without either hypertension or renovascular impairment.

It has been claimed repeatedly that an excess of epinephrine in the discharge of the suprarenal gland may increase blood pressure. One of

us [5] has shown in previous papers that the load of epinephrine in the suprarenals is increased in diseases associated with hypertension, such as chronic nephritis and arteriosclerosis. An increase in size of the suprarenals in such cases is almost constant, and so are changes in the structure of both the medulla and the cortex. In spite of these observations, it has not yet been generally accepted that the changes described prove conclusively the contention of a disturbed or excessive suprarenal function as the cause of hypertension and its sequelae.

Our results, however, based on measurable changes of the suprarenal veins, add new and weighty evidence to the theory which links hypertension and allied diseases with functional disturbances of the suprarenal glands.

SUMMARY

The musculature of the suprarenal veins was examined and measured in cases of hypertension, in cases of renovascular disease without evidence of hypertension and in cases without either hypertension or renovascular impairment. In the first and the second groups the musculature was hypertrophied, as compared to that of the third group.

Both the musculature of the central vein and the single muscle bundles of the small venules participated in the hypertrophy.

Injection of the suprarenals through the central veins in patients with hypertension revealed a different distribution of the injected dye from that in the controls.

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FAT CONTENTS OF PATHOLOGIC THYROIDS IN MAN

HISTOLOGIC STUDIES *

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The presence of lipoid droplets in the epithelium of the normal thyroid in man, and the excretion of these droplets into the colloid, suggest a study of the influence of pathologic changes in the gland on the amount and distribution of the fat. Previous investigations have shown that constant relations do not exist between diseases in general and the quantity of the lipoids demonstrable in the thyroid (Jaffé).[1] The literature on the fat content of diseased thyroids is scanty, and systematic examinations with the different fat staining methods, as far as I can determine, have not yet been reported.

The material used in this study consisted of two parenchymatous goiters (adolescent type), twelve colloid goiters, twenty exophthalmic goiters, twelve adenomatous goiters, three adenomatous and exophthalmic goiters, eight atrophic glands, one acute purulent thyroiditis, one chronic thyroiditis (Riedel's struma), one tuberculosis of the thyroid, one malignant adenoma and two adenocarcinomas. Most of the goiters, the Riedel's struma and the three malignant tumors were obtained by operation. The other changes were detected by the routine microscopic examination of autopsy material.

DIFFUSE PARENCHYMATOUS GOITER

The two glands belonging to this group had been removed from two girls, aged 14 years, who did not show any toxic symptoms. The glands exhibited the microscopic picture which Aschoff [2] describes as an exaggeration of the normal growth of the thyroid at puberty. Pool [3] speaks of a puberty hyperplasia, and Williamson and Pearse [4] group these cases under the heading "progressive vesicular goiter." Many small vesicles, lined by a high cuboidal epithelium, stained pale. Many vesicles con-

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tained a small drop of homogenous colloid; others appeared almost solid, with a narrow lumen. According to the youth of the proliferating cells, many of them had only a few fine fat granules along the internal margin. A small portion of the granules stained after the Lorrain-Smith potassium bichromate hematoxylin method. Here and there a single cell was found, filled with larger Lorrain-Smith-positive droplets. In the colloid were found a few spheroids with lipoid granules like those described in a previous publication. One gland also showed a number of free cells filled with fat droplets in the colloid.

COLLOID GOITER

Erdheim [5] found that the flattening of the epithelium in colloid goiters causes a decrease in the fat granules. Wegelin [6] says that the amount of fat in colloid goiters corresponds to the age of the patient. My observations are in accordance with Erdheim's statements; but even in extreme cases of epithelial flattening fat still is present. It appears as single larger droplets, at the side of the nucleus, bulging into the vesicular lumen. The microchemical reactions of the fat are the same as in normal thyroids. The majority of the droplets are stained black after the Lorrain-Smith method, and a number of droplets also take the Caccio's sudan III stain. In the colloid, spheroids with fat granules and groups of larger droplets are demonstrable. There are also free cells filled with lipoid droplets. They are not any more numerous than in normal glands. In the areas of proliferation or regeneration of growing colloid goiters the cylindric epithelial cells which line the cushion-like elevations of the wall are often rich in fat. The epithelium of the small vesicles inside these elevations contain much less fat. In the stroma of colloid goiters fat cells are as common as in normal glands. Varying numbers of migrating cells with fat granules of the same chemical composition as those in the epithelium and the colloid are also found.

EXOPHTHALMIC GOITER

In spite of many morphologic studies on the structural changes of the thyroid in exophthalmic goiter, relatively little attention has been given to the lipin content of the exophthalmic goiters. Sata,[7] who was the first person to give a detailed description of fat in goiters, mentions that both the atrophic and hypertrophic parenchyma contain much fat.

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6. Wegelin, C.: Schilddruese in Handbuch der speziellen pathologischen Anatomie, Berlin, Julius Springer, 1926, vol. 8.

7. Sata, A.: Ueber das Vorkommen von Fett in pathologischen Geweben, Beitr. z. path. u. z. allg. Pathol. **28**:461, 1900.

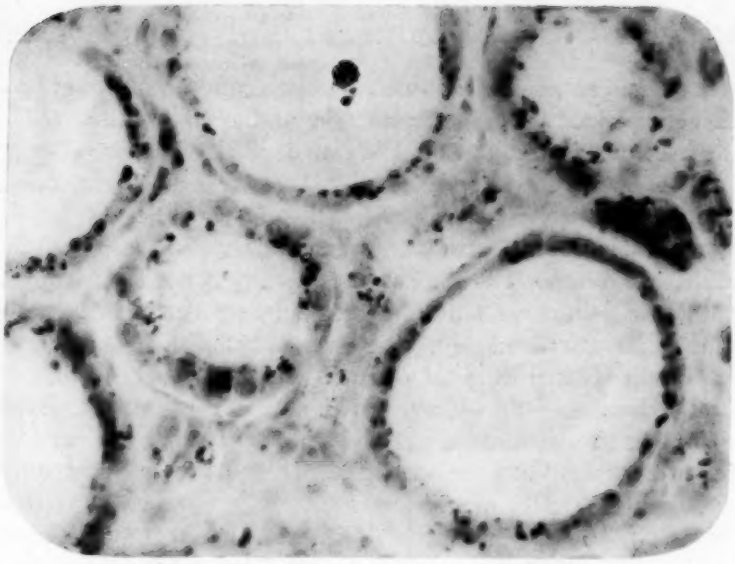

Fig. 1.—Area of normal thyroid tissue in an exophthalmic goiter; 10 per cent liquor formaldehydi, frozen section, hematoxylin-sudan III; magnification 470; the lipoid droplets in the vesicular epithelium and the granules in the vesicular content should be noted. Woman, aged 39; duration of symptoms, five months; loss in weight, 30 pounds (13.6 Kg.); slight exophthalmus; pulse rate, 100; basal metabolism rate day before operation, plus 34; 10 drops of compound solution of iodine three times a day for two and one-half weeks.

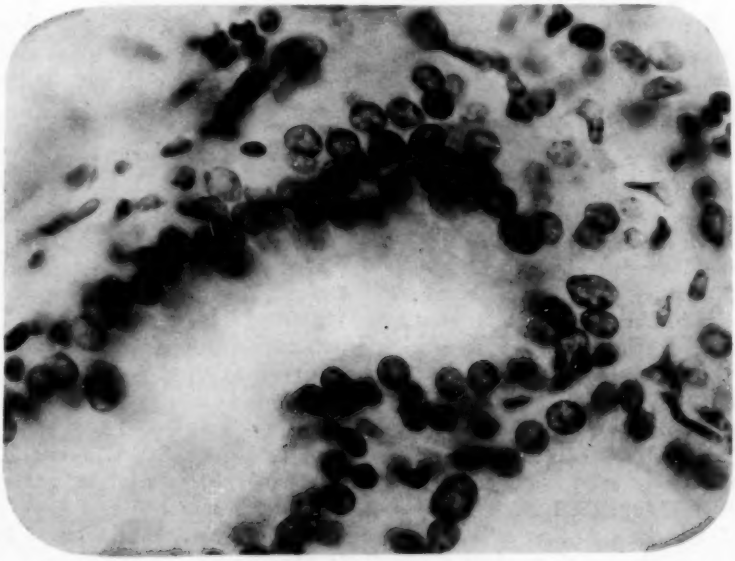

Fig. 2.—Another area of the thyroid shown in figure 1; technic same as in figure 1; magnification, 560; columnar epithelium showing beginning vacuolation of the cytoplasm; absence of fat from the epithelium and the vesicular content should be noted; the cytoplasm is not distinct in the photomicrograph, because it has remained almost unstained in the hematoxylin-sudan III section.

Erdheim found an irregularity of the fat content in exophthalmic goiters which he explained by the different ages of the proliferating cells. In the high columnar cells, many fine lipoid granules were present. A similar observation was made by Askanazy.[8] In eight cases of exophthalmic goiter, Pettavel[9] saw many fine granules of fat in the thyroid epithelium. Haeberli[10] says that fat is always demonstrable in exophthalmic goiters. The amount varies greatly. According to Holst,[11] exophthalmic goiters contain more fat than normal thyroids. Wegelin saw much fat associated with extensive epithelial desquamation. The cylindric cells showed little fat, because they were newly formed. The structural changes of the hypertrophic epithelial cells are not taken into consideration in any of these publications, nor is reference made to the lipoids in the colloid and the stroma. It is well known that the hypertrophic, cylindric cells of the exophthalmic goiters undergo changes which result, perhaps, from the different stages of their functional activity. The cylindric cells have a granulated cytoplasm, or they appear vacuolated, the vacuolation being most pronounced in the club-shaped part that bulges into the vesicular lumen. When the vacuolated part is masked off, the cells appear lacunar. According to Williamson and Pearse, this indicates their functional exhaustion.

In many of the glands which I studied, the microscopic picture had been influenced by the iodine medication received by the patients before the operation. Cattell,[12] Giordano,[13] Hellwig[14] and Rienhoff[15] showed that the iodine treatment recommended by Plummer brings about a return of the hyperplastic gland to the resting stage. The vesicles become round or oval. Colloid again fills their lumen. The papillary infoldings of the epithelium disappear, and the epithelium itself reassumes the low cuboidal shape. Areas are always left, however, in which the hyperplastic changes persist. I found that the extent of these areas

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8. Askanazy, M.: Pathologisch-anatomische Beitraege zur Kenntnis des Morbus Basedowii, Deutsches Arch. f. klin. Med. **61**:118, 1898.

9. Pettavel, C. A.: Beitraege zur pathologischen Anatomie des Morbus Basedowii, Deutsche Ztschr. f. klin. Chir. **116**:488, 1912.

10. Haeberli, E.: Ueber die morphologisch nachweisbaren Fettsubstanzen und die Oxydasereaktion in der menschlichen Thyroidea, Virchows Arch. f. path. Anat. **221**:333, 1016.

11. Holst, quoted by Wegelin (footnote 6).

12. Cattell, R. B.: The Pathology of Exopthalmic Goiter; Histological and Chemical Studies of the Changes following the Administration of Iodine, Boston M. & S. J. **192**:989, 1925.

13. Giordano, A. S.: Histologic Changes following Administration of Iodine in Exophthalmic Goiters, Arch. Path. **1**:881 (June) 1926.

14. Hellwig, A.: Jod bei Basedow, Klin. Wchnschr. **5**:2356, 1926.

15. Rienhoff, W. F.: Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter, Arch. Surg. **13**:391 (Sept.) 1926.

varies greatly, and that the amount of remaining hyperplastic tissue does not depend on the intensity and duration of the preceding iodine medication. I also made an observation similar to that of Cattell, namely, that there are a few instances of an increasing hyperplasia without apparent morphologic effect of the iodine. Finally, there were at my disposal a number of untreated exophthalmic goiters, found incidentally at postmortem examinations, which exhibited all the typical changes described by Müller,[16] Askanazy,[8] von Hansemann,[17] MacCallum,[18] Marine and Lenhart,[19] Kocher,[20] Wilson [21] and others.

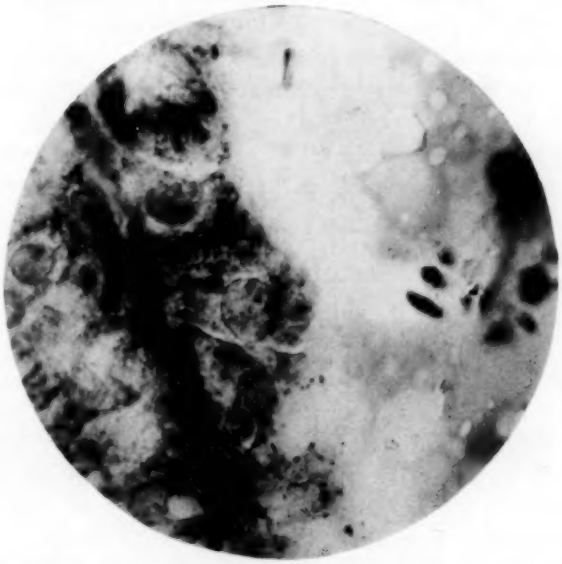

Fig. 3.—Columnar cell with irregular distribution of the lipoid granules; fixation same as in figures 1 and 2; Lorrain-Smith safranine stain; magnification, 800. Man, aged 41; exophthalmic goiter; duration about six months; pulse rate from 95 to 100; basal metabolism, plus 60; after twelve days' iodine treatment, day before operation, plus 35.

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16. Müller, L. R.: Beitraege zur Histologie der normalen und erkrankten Schilddruese, Beitr. z. path. Anat. **19**:127, 1896.

17. Von Hansemann: Schilddruese und Thymus bei der Basedowschen Krankheit, Berl. klin. Wchnschr., 1905, p. 65.

18. MacCallum, W. G.: The Pathology of Exophthalmic Goiter, J. A. M. A. **49**:1158 (Oct. 5) 1907.

19. Marine, D., and Lenhart, C. H.: The Pathological Anatomy of the Human Thyroid, Arch. Int. Med. **7**:506 (April) 1911; Pathological Anatomy of Exophthalmic Goiter, ibid. **8**:265 (Sept.) 1911.

20. Kocher, A.: Die histologischen und chemischen Veraenderungen der Schilddruese bei Morbus Basedow, Virchows Arch. f. path. Anat. **208**:86, 1912.

21. Wilson, L. B.: The Pathology of the Thyroid in Exophthalmic Goiter, Am. J. M. Sc. **146**:781, 1913.

The outstanding features in the microscopic lipin content of the exophthalmic goiters are as follows: the great irregularity in the distribution of the lipoid substances resulting from the structural changes of the hyperplastic epithelial cells, the disappearance of the fat with progressing vacuolation of the cytoplasm and its absence from the lacunar cells and the absence of lipoid carrying spheroids from the vesicular content.

The high cuboidal and cylindric cells with the granulated cytoplasm contain varying amounts of fat. The granules are small and scanty, and there are groups of cells free from fat. In only two of the twenty exophthalmic goiters were the granules numerous, or did they reach in places the size of the droplets in normal glands. In the cells with a club-shaped distention of the internal part, the lipoid granules do not show the typical arrangement along the internal margin. They are often distributed all over the cells and may even accumulate in the peripheral zone of the cytoplasm. The vacuolation of the cytoplasm leads to a complete disappearance of the lipin granules. First, a few ill-defined granules are still left. They stain pale with sudan III and remain unstained after the Lorrain-Smith method. Apparently, if the vacuoles decrease under the influence of the iodine treatment, the lipoid droplets become more distinct. Some glands contain single vesicles with an epithelial lining filled with fat droplets. The epithelial cells are often seen in desquamation, and many free cells full of lipoid substances are found in the lumen. The fat in the free cells stains after the Caccio method, while in other parts of the exophthalmic goiter this kind of lipoid material is scanty. In hyperplastic glands of longer duration, the majority of the desquamated cells are free from fat, even if their cytoplasm appears vacuolated. There are also cells with a homogenous waxy cytoplasm that stains diffusely yellow with sudan III.

The thin and vacuolated vesicular content often shows spheroids, but they do not carry lipoid granules. The clusters of larger droplets, too, are absent. Only in those places in which the normal structure of the thyroid has not yet been changed, or in which the hyperplasia has given way to the picture of the resting gland, the colloid contains lipoids.

Key[22] has described in the thyroid chromophile secretion antecedents which somewhat resemble lipoid granules, but which, as I believe, are different from the granules composed of phospholipins. The number of the chromophile secretion antecedents in exophthalmic goiters varies from less than normal to a marked increase. In addition, relations do not exist between the lipin granules and Altmann's granules and mitochondria. Mitochondria are numerous in exophthalmic goiters.

22. Key, J. A.: The Secretion Antecedents and Mitochondria in Pathological Thyroids, Arch. Surg. **11**:254 (Aug.) 1925.

In the stroma of exophthalmic goiters normal fat cells are rare. One may find in some glands many of the flat and branched fat carrying cells that are observed in normal thyroids. A staining of the plasma in the smaller blood vessels with sudan III was seen in 55 per cent of the exophthalmic goiters.

The differences in the fat content between the normal thyroid and the exophthalmic goiters speak in favor more of a dysfunction than of a hyperfunction of the thyroid in exophthalmic goiter. The complete absence of fat from certain cells is a sign not of their youth but of their functional exhaustion.

ADENOMATOUS GOITER

The nodular formations of proliferating thyroid tissue of which the so-called adenomatous goiters are composed always contain fat, whatever their structure may be. Erdheim found that the adenomas usually have less lipoids than the normal gland. Wegelin mentions that in follicular adenomas there may be so much fat as to obscure the structure. In general, there is not any relation between the amount of fat in the adenomas and that in the more or less normal tissue. In the marginal zone of compressed thyroid tissue around the adenomas, a local increase in fat is sometimes observed. Before taking up the lipoid content of the different types of adenomas I wish to emphasize that the regressive processes so commonly found in adenomas cause the appearance of fat which is degenerative in nature and which, according to the staining reactions, is different from the lipoid substances of the normal thyroid. In the degenerated areas, mixtures of neutral fat, cholesterol and cholesterol esters and free fatty acids are demonstrable.

In the trabecular types of adenomas which consist of solid cords of epithelial cells, the cells often show numerous fat droplets of different sizes. They stain black with the Lorrain-Smith hematoxylin technic, and there are also granules which are Caccio-positive. Some of the adenomas contain groups of cells with little if any fat, but adenomas in which the latter type of cells predominate are rare. The term fetal adenoma is still sometimes used for the purely cellular nodes in the thyroid. That this term is misleading is demonstrated by the result of the fat staining, because the fetal thyroid does not contain any fat.

In the adenomas formed by small vesicles the amount of fat varies much more than in the normal thyroid. In one microscopic field all the epithelial cells show a distinct line of small, medium-sized and large lipoid droplets. In the next field many of the epithelial cells may not show any fat.

With the increasing size of the vesicles the epithelium becomes flattened, and its fat content is markedly reduced. Many desquamated,

round cells stuffed with lipoid droplets are present in the lumen. The spheroids with smaller lipoid granules and the groups of larger droplets are also found. In some adenomas the colloid stains a diffuse yellow with sudan III. Buscaino [23] mentions the occurrence of sudanophil colloid in the enlarged acini of goiters, and suggests connections with hemorrhages. The cystic adenomas contain in their fibrous wall deposits of neutral fat, cholesterol esters and phospholipins.

In the stroma of adenomas fat cells are rare. The branched cells filled with small lipoid droplets are more numerous, especially in older nodules with a thickened stroma. The staining of the plasma in the smaller blood vessels with sudan III is noted also in adenomas. Since, however, the adenomas do not have sinuoid blood spaces, the staining is less distinct than in normal thyroids or in exophthalmic goiters.

The amount and character of the fat in simple adenomas are the same as in toxic adenomas. When the changes typical of exophthalmic goiter affect the glandular tissue of adenomas, the fat undergoes the same changes as it does in a previously normal gland.

ATROPHY OF THYROID

Eight glands, the weight of which was about half the normal, namely, from 15 to 17 Gm., were studied. There was not any case of myxedema. The senile atrophy of the thyroid was not included. The atrophic glands were obtained from cachetic patients who had died from malignant tumors or chronic infections, chiefly tuberculosis. Contrary to Krieger,[24] I made the observation that tumor cachesia leads to a reduction of the size and weight of the thyroid. The vesicles of the atrophic glands were small and filled with thick homogenous, partly basophilic colloid. The epithelial cells were low and cuboidal, and the interstitial tissue was increased, but loose. The lipoids did not show any differences from normal thyroids. In two glands removed from persons under 30 years of age the epithelium was rich in fat.

THYROIDITIS

The fat content of the thyroid epithelium and of the colloid, at first, is not affected by inflammatory changes in the interstitial tissue. Not until the vesicles are destroyed do the fat droplets disappear. In a case of metastatic purulent staphylococci thyroiditis many lipoid droplets were seen in the epithelium of the vesicles bordering at abscesses. The breaking of the pus into the vesicles caused necrosis of the epithelium and loss of the lipoid granules.

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23. Buscaino, quoted from Vercelli: Studies of the Thyroid and its Qualitative Variations, Endocrinology **4**:88, 1920.

24. Krieger, quoted from Wegelin (footnote 6).

In the case of chronic thyroiditis (Riedel's struma) the gland consisted mainly of a granulation tissue with dense accumulations of lymphocytes, which by their arrangement often resembled lymph follicles. Many plasma cells and huge giant cells with as many as fifty nuclei were also present. Groups of vesicles were embedded with the granulation tissue. Their lining was cuboidal and their content was formed by homogenous colloid. The epithelium contained groups of small lipoid granules and larger droplets, which were extruded into the colloid. Some vesicles were filled with free round cells the vacuolated cytoplasm of which was either filled with fat or free from it. Areas of regeneration were seen, with small and irregularly shaped vesicles, lined by a dark nucleated columnar epithelium. In these newly formed cells, too, many fat droplets were present. As shown by the fat staining the giant cells developed from the vesicular epithelium by fusion. In the early stages of the giant cell formation, fat droplets were found in the center of the cells. They stained black after the Lorrain-Smith method. In the larger cells, fat was not demonstrable.

Only one gland was completely devoid of lipoid material. It contained a large, solitary tubercle and was found in a boy, aged 12 years, who had died from a chronic tuberculous peritonitis.

CARCINOMA OF THE THYROID

In the malignant epithelial tumors of the thyroid fat could not be detected in the sections stained after the Lorrain-Smith and Caccio technics. In the sudan III sections, too, most of the anaplastic cells were free from fat. Where regressive changes had taken place, fat was present. It gave the microchemical reactions of neutral fat. Outside the carcinomatous areas, the thyroid epithelium showed much fat, which was given off into the colloid.

COMMENT

The amount of demonstrable lipoids varies greatly in thyroids which appear normal microscopically. What may influence the lipoid content is difficult to determine. In older people, the glands with much fat are more common than in young persons, but under apparently the same conditions (age, nutrition, diseases, cause of death) one can find all degrees from a fine and scanty granulation to a great many large droplets. It has been suggested in a preceding paper that the lipoid granules are secretory products of the thyroid epithelium and that the number and size of the granules may, to a certain degree, indicate the functional activity of the gland. Middle aged persons who die suddenly without previous illness have, as a rule, thyroids with many lipoid droplets in the epithelium and in the colloid. Glands with little fat, after the twentieth year of life, are not normal, although they may not

show any anatomic lesions. The decrease in fat is the result of diseases. There are, however, great differences as to the extent of this decrease at the time of the death.

Under various pathologic conditions located in the thyroid itself the epithelium retains its lipoid granules and continues excreting them into the colloid. Inflammatory processes affect the lipoid content only if they lead to a destruction of the vesicles. The amount and distribution and the chemical nature of the fat in the diffuse simple goiters do not differ from the normal gland. The adenomas may show more or less fat than the rest of the gland. In the vesicular nodes the segregation and excretion of the lipoids takes place in the same manner as it does in the normal thyroid. In the nodes composed of solid cords of cells much fat may pile up, since there is little possibility to excrete it. In two instances the lipoid content of the thyroid appeared to be much altered, namely, in exophthalmic goiter and in carcinomas of the thyroid. The columnar cells of exophthalmic goiters with a granulated cytoplasm may show fat in places. Rarely, however, do they contain as much fat as the normal gland. The granules are not extruded into the lumen. They become distributed over the entire cell, and when vacuolation sets in they disappear. The vacuolation of the epithelium, therefore, seems to be a sign of functional exhaustion. When under the influence of iodine the glandular epithelium reassumes the normal appearance, the fat granules reappear also.

The cells of carcinomas of the thyroid do not secrete any lipoids. The fat that is demonstrable in carcinomas results from degenerative changes and is chiefly neutral fat.

SUMMARY

Sixty-three thyroids in man with various pathologic changes were studied for their microscopic fat content.

Simple, diffuse, parenchymatous and colloid goiters do not markedly differ in their lipoid content from the normal thyroid.

Adenomas are usually rich in fat. Relations do not exist between the fat content of the adenomas and that of the remaining thyroid tissue.

Inflammatory changes affect the lipoid segregation and excretion of the thyroid epithelium only when they lead to a destruction of the vesicles.

In exophthalmic goiters the fat is usually decreased. This decrease is most pronounced in the areas composed of vacuolated cells. Extrusion of lipoid droplets into the vesicular lumen does not occur.

The malignant epithelial tumors of the thyroid contain only fat that results from degenerative changes.

VASCULAR LESIONS OF PORTAL CIRRHOSIS *

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In the last two years the most distinct advance made in the treatment for ascites of portal cirrhosis has been the introduction of the newer diuretics. Keith and Whelan [1] have shown that following the intravenous administration of merbaphen combined with the simultaneous use of ammonium chloride or ammonium nitrate, the ascites can be well controlled for long periods. There comes a time, however, when not even this palliative measure suffices, and the patients succumb to one or another of the many complications to which they are especially susceptible. Under these circumstances, cases have been encountered at necropsy in which unusually advanced hepatic injury was noted because the patients had survived for longer periods; especially has there been a striking increase in the fatal lesions of the vascular system. Preble,[2] in 1900, in a report of sixty fatal cases of gastro-intestinal hemorrhage, considered it an infrequent, but not rare, complication of cirrhosis. In 80 per cent of his cases esophageal varices were present, and in half of these macroscopic ruptures were found. Preble adds that many more varices and perforations would be discovered if fluids were injected to detect them. Blumenau,[3] in 1920, reported that of 126 patients affected with obvious portal cirrhosis at the time of death, 19 per cent died from vascular lesions and 19 per cent from the cirrhosis itself. My own figures show that there was a fatal gastro-intestinal hemorrhage in thirteen (50 per cent) of the last twenty-six patients who died of advanced portal cirrhosis. Besides this group there appears to be an increasing number of patients who, having been steered safely past the Scylla and Charybdis of hemorrhage and ascites, succumb to hepatic insufficiency. As I shall attempt to show, this, too, is probably of vascular origin. It is therefore manifest that if a specific is lacking, any further efforts in palliative treatment must be directed toward the vas-

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1. Keith, N. M., and Whelan, Mary: A Study of the Action of Ammonium Chlorid and Organic Mercury Compounds, J. Clin. Investigation **3**:149, 1926.

2. Preble, R. B.: Conclusions Based on Sixty Cases of Fatal Gastro-Intestinal Hemorrhage Due to Cirrhosis of the Liver, Am. J. M. Sc. **99**:263, 1900.

3. Blumenau, Ernst: Ueber Todesursache bei Lebercirrhose, Arch. f Verdauungskr. **27**:1, 1921.

cular system. With this in mind an exhaustive examination has been made of the material obtained at necropsy from those patients who were treated with the newer diuretics and who died with full-fledged portal cirrhosis, particular attention being given to the intrahepatic and extrahepatic portions of the portal venous system. An effort has also been made to correlate the vascular alterations with those in the hepatic parenchyma and to emphasize the physical and mechanical factors in the development of ascites.

Since Kretz [4] and McCallum [5] demonstrated the regenerative features of portal cirrhosis, little of importance has been added to the classic descriptions of Laennec [6] and Charcot.[7] The latter in particular described the vascular changes with great clarity. While most authors have agreed on the sclerosing effect of the cirrhotic process on the intrahepatic blood vessels, this part of the venous system has been the least satisfactorily studied. Sabourin [8] and Hess [9] believed that endophlebitis, periphlebitis and thrombosis played an extensive part in the obliteration of the vascular bed, while Kretz explained the phenomenon rather on the basis of a simple obliterative sclerosis. The extrahepatic portal system has in all respects been more carefully examined, especially by Dusaussay,[10] Chautemps,[11] Gilbert and Villaret [12] and others. Most of these writers emphasize the importance of esophageal varices in gastro-intestinal hemorrhage and point out the serious prognostic significance of this complication.

A variety of methods was used in examining the material from sixteen cases of Laennec's cirrhosis, in all of which ascites was present in greater or lesser degree. Injections of gelatin and india ink into the

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4. Kretz, Richard: Cirrhosis of the Liver, Internat. Clin. **3**:289, 1905.

5. MacCallum, W. G.: Regenerative Changes in Cirrhosis of the Liver, J. A. M. A. **43**:649 (Sept. 3) 1904.

6. Laennec, R. T. H.: Traité de l'auscultation médiate et des maladies des poumons et du coeur, Paris, J. S. Chaudé, 1826.

7. Charcot, J. M.: Leçons sur les maladie du foie des voies biliares et des reins. Progrès méd. 1877, pp. 380.

8. Sabourin, C.: Considérations sur l'anatomie topographique de la glande biliare de l'homme, Rev. de méd. **2**:40, 1882; Du rôle que joue le système veineux sus-hépatique dans la topographie de la cirrhose du foie, ibid. **2**:465, 1882.

9. Hess, A. F.: Fatal Obliterating Endophlebitis of the Hepatc Veins, Am. J. M. Sc. **130**:986, 1905.

10. Dusaussay, M.: Étude sur les varices de l'oesophage dans la cirrhose hépatique, Thésis de Paris, 1877.

11. Chautemps, E.: Des hémorrhagies dans la cirrhose du foie, Thésis de Paris, 1875.

12. Gilbert, A., and Villaret, Maurice: Les circulations veineuses supplémentaires de la paroi thoraco-abdominale antérieure, en particulier au cours des affections hépatiques, Rev. de méd. **27**:305, 1907.

portal vein in situ were found satisfactory for the demonstration of the portal circulation in general with its collateral anastomosis. An attempt was made to estimate the effect of the sclerosing process on the flow of the portal blood by perfusion of the portal vein with physiologic sodium chloride solution, after the method of Herrick.[13] The corrosion method previously described by Counseller and McIndoe[14] for the bile ducts was used in demonstrating the intrahepatic vascular changes, supplemented by reconstructions of wax, both of the vessels and fibrous tissue and of the parenchyma. A large number of normal livers used as controls were also examined by the same methods.

Before the changes occurring in cirrhosis are considered, it would be well to review a few salient points in anatomy and physiology which have a bearing on the question under discussion. Corrosion specimens of the portal vein show that it consists of a massive system of branches ascending directly without cross-anastomosis through five or six successive orders of division to the sinusoidal circulation. In general, the branches are given off at right angles to the parent stem, while the sinusoids themselves arise from the tips of the venules (Mall[15]). The hepatic artery lies in close relationship to the portal vein within the portal space and occasionally winds around it (fig. 1 *A*). Three distinct groups of branches arise from the artery. The vaginal branches form an intricate arteriolar plexus in the connective tissue of the portal space and undoubtedly are its main source of nourishment. They apparently end in capillaries which communicate with both the portal vein and with the intercellular sinusoids. The vascular branches end directly in the sinusoids at the periphery of the portal spaces. The capsular branches form an arteriolar anastomosis over the capsule and communicate with the phrenic, internal mammary, renal and suprarenal arteries. The vein supplies 60 and the artery 40 per cent of the hepatic blood (MacLeod and Pearce[16]). By a delicate nervous mechanism derived from the splanchnics and located chiefly around the hepatic artery, the small arterial stream under high pressure and the large venous stream under low pressure are reduced to a common level at the commencement of the sinusoidal bed. The experiments of Burton-

13. Herrick, F. C.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93, 1907.

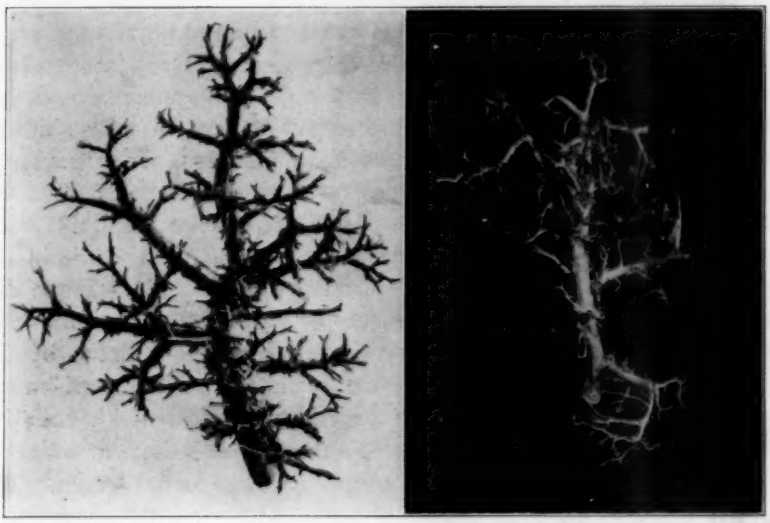
14. Counseller, V. S., and McIndoe, A. H.: Dilatation of the Bile Ducts (Hydrohepatosis), Surg. Gynec. & Obst. **43**:729, 1926.

15. Mall, F. P.: A Study of the Structural Unit of the Liver, Am. J. Anat. **5**:227, 1906.

16. MacLeod, J. J. R., and Pearce, R. G.: The Outflow of Blood from the Liver as Affected by Variations in the Condition of the Portal Vein and Hepatic Artery, Am. J. Physiol. **35**:87, 1914.

Opitz [17] have shown that there is an intricate functional relationship between the arterial and venous circuits, such that the former may become a highly important compensatory factor whenever the portal inflow is lessened or entirely obstructed.

The hepatic veins have much in common with the portal veins. They, too, form a massive system of branches commencing at the central veins and passing through the sublobular veins to the inferior vena cava by five or six successive orders of division. There are, however, certain distinguishing characteristics. The central veins receive their tributary sinusoids from the parenchyma throughout their whole length, unlike



A B

Fig. 1.—*A* shows a celloidin cast of a small branch of the portal vein and hepatic artery from a normal liver. The vaginal arterial plexus is well shown (reduced from a magnification of × 3). *B* shows a celloidin cast of a small branch of the portal vein in a case of atrophic portal cirrhosis (reduced from a magnification of × 3).

the portal veins, which give off their sinusoids only from their extreme tips. The hepatic vein runs entirely alone and is surrounded by parenchyma throughout its course, with the intervention of a small amount

17. Burton-Opitz, Russell: The Vascularity of the Liver: I. The Flow of the Blood in the Hepatic Artery, Quart. J. Exper. Physiol. **3**:297, 1910; II. The Influence of the Portal Blood Flow Upon the Flow in the Hepatic Artery, ibid. **4**:93, 1911; III. The Effect of Stimulation of Single Nerves of the Hepatic Plexus Upon the Flow in the Hepatic Artery, ibid. **4**:103, 1911; IV. The Magnitude of the Portal Inflow, ibid. **4**:113, 1911; V. The Influence of the Greater Splanchnic Nerves Upon the Arterial Inflow, ibid. **5**:83, 1912; VI. The Motor Reaction of the Portal Radicles of the Liver, ibid. **6**:57, 1914.

of perivascular connective tissue, an extension of the fibrous tissue of the portal spaces. There is no anastomosis either with the portal vein or with the hepatic artery except through the sinusoidal bed, and the two venous systems are always separated by parenchyma. This relationship is shown much better by double injections of the portohepatic venous trees and by wax reconstructions of the finest branches in conjunction with the intervening hepatic cell mass. The extraordinarily regular arrangement of the vascular terminals is then made clear (fig. 2 *A*). Each central vein lies midway between any two corresponding portal terminals at a distance representing half the diameter of the so-called hepatic lobule. Because of this, the cell mass assumes a certain foliated or lobulated appearance. It is also by reason of this entirely vascular phenomenon, and by an analogy with the anomalous

A B

Fig. 2.—*A* shows a celloidin cast of the portal (dark) and hepatic (light) venous trees from a normal liver showing the regular arrangement; *B*, the same in a case of portal cirrhosis showing complete disorganization of the normal arrangement.

livers of such animals as the pig and the polar bear, that the liver of man has come to be regarded as composed of separate units or lobules. Such is not the case. The area of parenchyma drained by a central vein is by no means defined by connective tissue, nor is it in any sense a structural unit, although the conception has been found convenient in the conventional method of studying the liver, that is, by two dimensional cross-sections. Serial sections and wax reconstructions show at once that the hepatic venous tree is clothed from the central vein to the inferior vena cava in a continuous sheet of hepatic parenchyma regularly and alternately pierced, supplied and drained by the terminals of the portal and hepatic veins. Each of the tiny masses of tissue so defined is continuous with the adjacent one by free sinusoidal and bile canalicular intercommunication and shows no trace of a fibrous capsule. To satisfy

those who may object on embryologic grounds, the same conception also applies to the portal vein, since it may also be regarded as clothed from the terminals to the trunk by the hepatic cell mass. There are thus grave objections to the so-called lobules of Kiernan,[18] Sabourin [8] and Mall.[15] In short, therefore, the liver contains two huge venous trees dovetailing into each other so regularly and exactly that no two vessels come in contact and all terminals are at the greatest possible distance from each other. The intervening space is occupied by hepatic cells. By this means the maximal amount of portal blood in its path to the hepatic vein is exposed to as much of the parenchyma and for as long as possible. This conception, first advanced by Kretz [5] and firmly upheld by Kelly [19] and Epplen,[20] is of the greatest value in following the changes occurring in cirrhosis. The portohepatic venous arrangement seems particularly important in relation to the development of ascites.

THE CHANGES IN THE INTRAHEPATIC BLOOD VESSELS IN CIRRHOSIS

An examination of corrosion specimens from six cases of portal cirrhosis throws considerable light on the condition of the intrahepatic vessels. One of the most superficially obvious changes is the marked diminution in the total hepatic vascular bed. By a comparison of the portohepatic venous system of a normal liver weighing 1,600 Gm. with that in a case of marked atrophic cirrhosis weighing 900 Gm., it can be seen that both trees in the latter are greatly diminished in size and are equally affected (fig. 3). The main trunks are attenuated and irregularly stenosed, having lost that appearance of robust strength so notable in the normal vessels. Their larger branches are given off at unusually abrupt angles and occasionally show irregular deviation to one side or the other as though pushed or pulled by an invisible force. It is among the finer branches, however, that the more profound alterations are to be seen. The tiny portal veins are distorted beyond belief, twisted and curled on themselves, and finally broken up into a network of stunted venules from which irregularly scattered terminals arise (fig. 1 *B*). In the tree of the hepatic vein the same change is found, its extent varying with that of the corresponding portal vein. It is usually difficult to detect any normal central veins whatever, especially if the cirrhosis is far advanced. Contrary to Kretz, I have not noted constant

18. Kiernan, F.: The Anatomy and Physiology of the Liver, Phil. Tr., Lond. **73**:711, 1833.

19. Kelly, A. O. J.: The Nature of the Lesions of Cirrhosis of the Liver with Special Reference to the Regeneration and Rearrangement of the Liver Parenchyma, Am. J. M. Sc. **130**:951, 1905.

20. Epplen, Frederick: The Pathology of Cirrhosis of the Liver, Arch. Int. Med. **29**:482, 1922.

enlargement of the hepatic artery, this vessel appearing to share in the general atrophy. The total loss of the normal regular portohepatic venous relationship is perhaps the most striking feature. The terminals of the two systems no longer alternate with one another, but tend to lie together and to assume a basket-like arrangement. This leaves irregu-

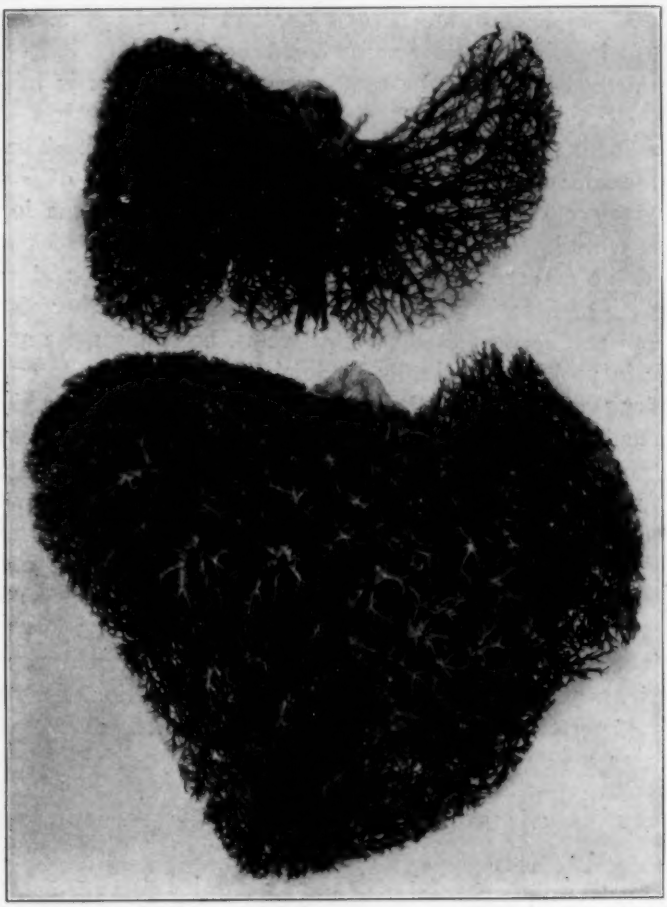


Fig. 3.—Celloidin casts of portohepatic venous trees in normal liver (lower) and in advanced portal cirrhosis (upper). Note the marked reduction in total vascular bed.

lar circular spaces obviously occupied by regenerated nodules of hepatic cells and entirely devoid of venous channels capable of injection with the celloidin mass (fig. 2 *B*). Such injections also show that all the collaterals arising from the liver itself come from the portal veins before their terminals are reached. The actual situation of the blood vessels with regard to the parenchyma can be determined by injections of gela-

tin and India ink into the portal and hepatic veins. In the terminal stages they lie entirely buried in the fibrous-tissue bands surrounding the nodules of hepatic tissue, although occasionally a small venule in the cell mass is filled with the material injected. As a rule, the nodules remain entirely uninjected. The same condition can be shown by means of wax models of the fibrous tissue reconstructed apart from the parenchyma. These demonstrate beyond question the almost total divorce of the hepatic cells from their portal blood supply.

The method by which the vessels reach this position is fairly well known. It can easily be followed by injections of gelatin into the hepatic veins of livers in different stages of the condition. The microscopic appearance then indicates that as destruction of areas of parenchyma occurs the resulting deficiency and fibrous-tissue formation bring the central veins closer to the portal spaces about which the connective tissue gathers in the early stages. Concomitant and repeated regeneration of hepatic cells and tortuous capillaries further distort the hepatic-cell mantle, so that the central veins, becoming more and more eccentric in position, eventually lie in the peripheral bands of fibrous tissue along with the portal veins. The further change which both systems undergo is then the same as that of vessels in scar tissue elsewhere. A slow obliteration of the smallest radicles by simple pressure atrophy and degeneration is observed, the tendency being toward the production of an avascular scar. Although many observers have found evidence of obliterative endophlebitis or periphlebitis and occasional thrombosis to account for the vascular disappearance, I do not believe that the process differs in any respect from that which takes place in simple inflammatory repair. As here, the veins are lost first, whereas the arteries persist longer. The sum total is the production of a gradually increasing portohepatic venous obstruction which may eventually become complete.

EFFECT OF CIRRHOSIS ON THE SUPPLY OF BLOOD OF THE PARENCHYMA

As I have stated, the ultimate and combined effect of degeneration and regeneration of the parenchyma and the progressive sclerosis is to produce a complete rearrangement of the vessels and the intervening hepatic-cell mantle. Instead of lying in a continuous sheet between the portal and hepatic venous trees and in the direct pathway of the afferent and efferent blood vessels, the hepatic-cell mantle is now broken up into innumerable irregular independent and anastomosing nodules, virtually all new formations, consisting of twisted columns of cells with narrow tortuous sinusoids, without a suggestion of the usual radiate arrangement. Buried in dense fibrous tissue, they are almost completely sidetracked from the supply of portal blood and obtain their nutriment in an

exceedingly inefficient manner. The nature and amount of their nutrient supply may be measured in a variety of ways. Injections of colored gelatin through the portal vein leave the nodules entirely uncolored, but through the hepatic artery they may be reached with slight difficulty. It would seem, therefore, that the reamaining parenchyma is dependent on the hepatic artery for almost its entire supply of blood. This is analogous

Perfusion Experiments on Livers Showing Advanced Portal Cirrhosis and Ascites

Case	Vessel Perfused	Pressure Mm. of Mercury	Duration	Amount Perfusion Cc.	From Hepatic Vein		Amount of Solution Recovered: From Portal Vein		From Collateral Vessels	
					Cc.	Per Cent	Cc.	Per Cent	Cc.	Per Cent
	Physiologic Sodium Chloride Solution at 37 C.									
1	Portal vein *	10	?	†	†	..	.....		†	..
		15	?	†	†	..	.....		†	..
		20	7.00 min.	1000	50	5	Perfused		950	95
		30	5.00 min.	1000	70	7	Perfused		930	93
		40	2.50 min.	1000	88	8	Perfused		912	91
		50	2.00 min.	1000	90	9	Perfused		910	91
		60	1.50 min.	1000	105	10	Perfused		895	89
		70	1.50 min.	1000	105	10	Perfused		895	89
		80	1.25 min.	1000	114	11	Perfused		886	88
		110	1.00 min.	1000	136	13	Perfused		864	86
2	Portal vein	10	15.00 min.	630	†	..	Perfused		630	100
		110	1.00 min.	1000	136	13	Perfused		864	86
		30	4.50 min.	1000	110	11	Perfused		890	89
		40	3.20 min.	1000	180	18	Perfused		820	82
		50	1.55 min.	1000	240	24	Perfused		760	76
		80	1.25 min.	1000	300	30	Perfused		700	70
		110	1.00 min.	1000	325	32	Perfused		675	67
	Hepatic artery	160	12.00 min.	1000	†	..	200		760	76
3	Portal vein	10	20.00 min.	50	†	..	Perfused		50	100
		20	15.00 min.	500	50	10	Perfused		450	90
		30	4.30 min.	1000	200	20	Perfused		800	80
		40	3.45 min.	1000	225	22	Perfused		760	76
		50	2.00 min.	1000	310	31	Perfused		710	71
		60	1.00 min.	1000	350	35	Perfused		650	65
		80	50.00 sec.	1000	350	35	Perfused		650	65
		110	40.00 sec.	1000	400	40	Perfused		600	60
	Hepatic artery	80	6.00 min.	1000	525	53	15	2	450	45
		110	4.00 min.	1000	525	52	25	2	450	45
		160	3.00 min.	1000	500	50	30	3	460	40
4	Portal vein *	10	9.25 min.	1000	120	12	Perfused		860	86
		20	5.40 min.	1000	130	13	Perfused		870	87
		30	3.50 min.	1000	145	14	Perfused		850	85
		40	2.25 min.	1000	150	15	Perfused		850	85
		50	1.56 min.	1000	200	20	Perfused		800	80
		60	1.29 min.	1000	220	22	Perfused		790	79
		80	1.00 min.	1000	300	30	Perfused		700	70
		110	0.37 min.	1000	340	34	Perfused		650	65

* Hepatic artery too small to inject in this case.
† Flow could not be induced.

to what occurs in the presence of metastatic nodules of carcinoma in the liver. The portal veins disappear and the arteries form almost their sole source of supply. A more convincing and accurate method of measuring this effect is to remove the liver from the cadaver as carefully as possible and to inject physiologic sodium chloride solution into the portal vein or hepatic artery at different pressures. The time taken by a measured amount to pass through the organ is noted, and the amounts returned from the hepatic vein and collateral channels are

collected and measured. The results obtained with four livers showing the most advanced grade of portal cirrhosis are tabulated.

While these experiments are performed on dead tissues and therefore questions of nervous control and other intra vitam conditions are not taken into consideration, the results are so absolute as to be of considerable value. They show, for instance, that at the probable pressure in the portal vein in cirrhosis, that is, between 10 and 20 mm. of mercury, from 86 to 100 per cent of the fluid passes directly into the collateral circulation. Thirteen per cent is the most that is recovered from the hepatic vein, in some cases none, in contrast to 100 per cent in the normal liver. As the intrahepatic collaterals are given off the portal vein before the sinusoidal bed is reached, it is certain that none of the fluid recovered from these channels comes in contact with the hepatic parenchyma, since it is shunted as through a by-pass before it reaches its normal destination. Some of the fluid recovered from the hepatic veins may or may not have passed through the nodules of hepatic cells, but even if all of it did, the amount would be extremely small. Another point of interest is that the time taken to inject the fluid at these low pressures is exceedingly long, almost ten times as long as in such an experiment on normal livers. The difficulty with which it passes and the fact that higher pressures are required to obtain a free flow seem to show conclusively not only that a definite portohepatic venous block exists per se, but that the supply of portal blood in the parenchyma is reduced to a minimum, if it is not absent altogether.

The results from the same procedure when applied to the hepatic artery are a little more difficult to evaluate and are somewhat untrustworthy. Fluid returns by both the portal and hepatic veins as well as by the collateral vessels. The most outstanding feature is that a much higher percentage returns through the hepatic vein than after perfusion into the portal vein. Presumably, this additional amount traverses the hepatic sinusoids, an observation in harmony with my experiments with gelatin. An attempt to duplicate the work of Herrick by perfusion into the vein and artery simultaneously under their respective normal pressures, failed entirely. The results were so inconstant and the effect was so slight as to make negative, in my own mind at least, the possibility that the high pressure arterial stream entering the low pressure venous stream in such a condition as cirrhosis could produce enough back pressure to be the chief factor in portal obstruction and the production of ascites. This can be entirely explained on a physical basis of portohepatic venous obstruction.

It seems safe to conclude, therefore, that in advanced cases the liver is virtually in the condition of having an Eck fistula between the portal vein and the inferior vena cava, and that the task of supplying sufficient blood to the parenchyma for normal metabolism is relegated to the

hepatic artery. When even this mechanism fails, the patient dies from hepatic insufficiency due to an insufficient supply of blood to the parenchyma, rather than to an actual deficiency in amount of hepatic tissue. From the experiments of Mann and his associates, it is certain that an exceedingly small amount of hepatic tissue properly nourished is

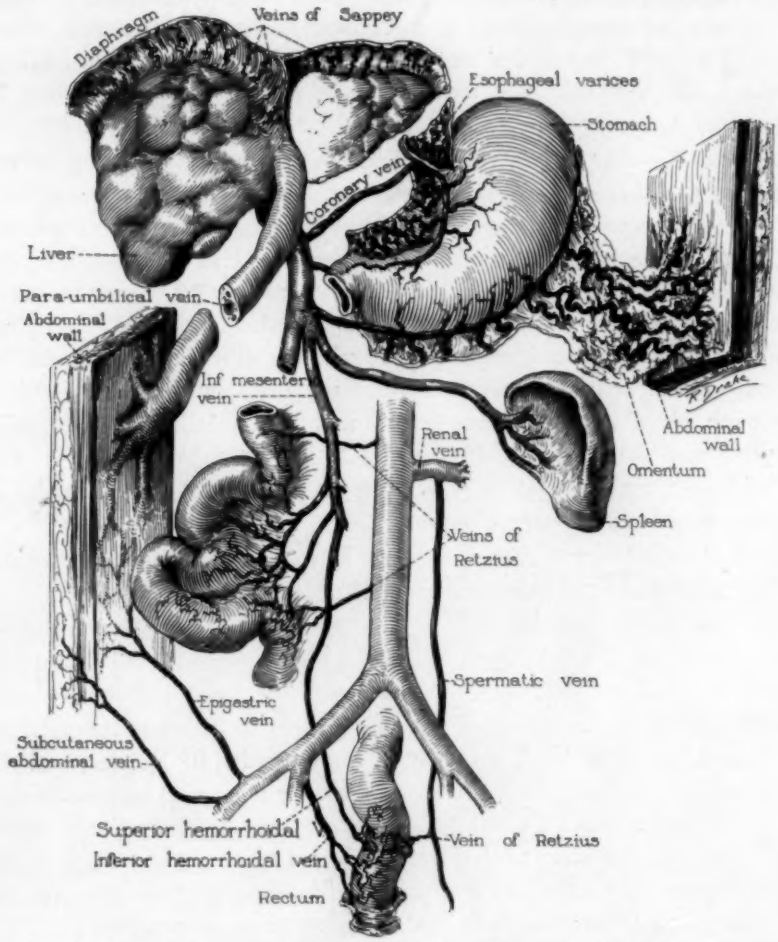


Fig. 4.—Schematic representation of the collateral circulation in portal cirrhosis.

required for normal metabolism, much less in fact than is present in the most advanced cases of portal cirrhosis.

COLLATERAL CIRCULATION

Coincident with the obliteration of the portohepatic venous pathway, collateral channels are gradually opened between the portal and caval systems. Such channels are, of course, developed at points at which

contact between the two systems already exists potentially. Their situations are well known and require little comment. A combined schematic representation is given of the results obtained from injecting the whole portal system in situ with gelatin and India ink in five cases (fig. 4). In classifying these rather numerous channels, I have adopted a method given me by Dr. H. A. Harris of University College, London. It has the advantage of being embryologic in conception and consequently easier to remember than the formidable anatomic lists in textbooks. The channels fall naturally into three groups, according to situation:

Group 1.—At the two situations in the gastro-intestinal tract where absorbing epithelium comes in contact with protective epithelium, that is, the cardia and the anus. The former represents the site of anastomosis of the coronary vein of the stomach with the intercostal, azygos minor and diaphragmatic veins of the caval circulation, here producing esophageal varices. At the latter, the superior hemorrhoidal vein of the portal circulation anastomoses with the middle and inferior hemorrhoidal veins of the caval circulation. Occasionally hemorrhoids develop, although they rarely become large and are usually not clinically important.

Group 2.—At the site of an obliterated embryologic circulation, that is, the falciform ligament containing the parumbilical veins. The umbilical vein is itself rarely, if ever, a part of the actual circulation. being entirely obliterated a few days after birth.

Group 3.—At all situations within the abdomen where the gastro-intestinal tract, its appendages or the glands developed from it, become retroperitoneal developmentally or adherent to the abdominal walls pathologically. This includes the duodenum, small intestine, colon, omentum, spleen and pancreas, containing the veins of Retzius, and the liver with its accessory veins of Sappey, both establishing an anastomosis between the portal and caval veins. These channels may be increased artificially by operative procedures, as for instance by producing adhesions between the liver and diaphragm or by attaching the omentum to the anterior abdominal wall, as in the Talma-Morison operation.

A survey of the cases of portal cirrhosis in which I made injections and of others examined in routine manner at necropsy shows that while in certain cases there is no enlargement of the collateral circulation and in others which have never been associated with ascites this circulation is increased, the condition is constantly present wherever persistent ascites has been clinically demonstrable. Occasionally, however, such vascular short-circuiting may be overlooked for the reason that not all the possible anastomotic routes are utilized, and that those opened up

are not all involved to the same degree in any one case. Thus the retroperitoneal veins may be enormously enlarged, while the parumbilical veins remain normal in size. The latter at other times may be converted into huge channels capable of accommodating the whole flow of portal blood, with little evidence of collarteral dilation elsewhere. In such cases the veins of the anterior abdominal wall are prominent, and there is a well marked caput medusae. In all cases, however, in which

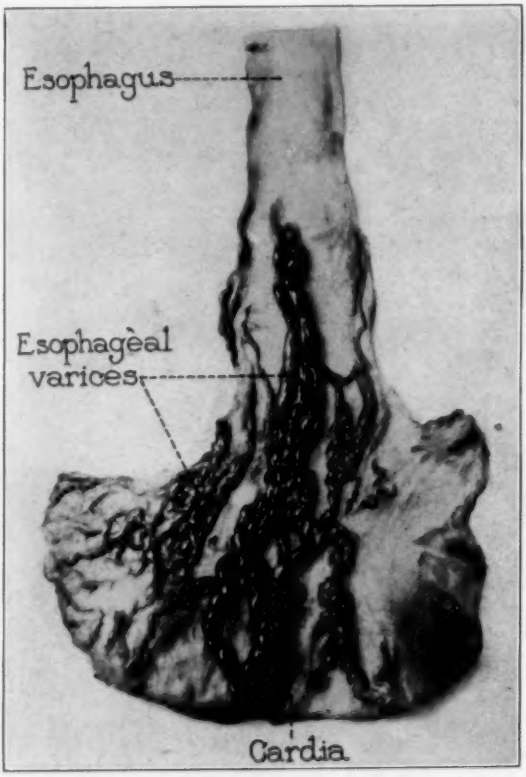


Fig. 5.—Esophageal varices injected with gelatin and India ink in a case of portal cirrhosis. The mucosa is stripped off.

gastro-intestinal hemorrhage has occurred, careful examination either by inflation or by injection invariably reveals well developed esophageal varices.

The relationship of hemorrhage to the esophageal varix is of such importance as to warrant considerable attention. In spite of the fact that patients occasionally have died of hemorrhage in which varices could not be demonstrated, and the hemorrhage was considered to be diffuse capillary bleeding from the gastric mucosa, it is believed that a more careful examination would have disclosed them. Even in the

most marked cases the veins collapse after death and are practically invisible beneath the squamous epithelium of the esophagus. The point of rupture, too, is usually insignificant and for this reason, the varices are often overlooked. Nevertheless, if inflation or injection is resorted to, the varices stand out with startling prominence, and the bleeding point is usually clear. They are situated in the lower three fourths of the esophagus and close to the cardia, and occur both in the submucosal

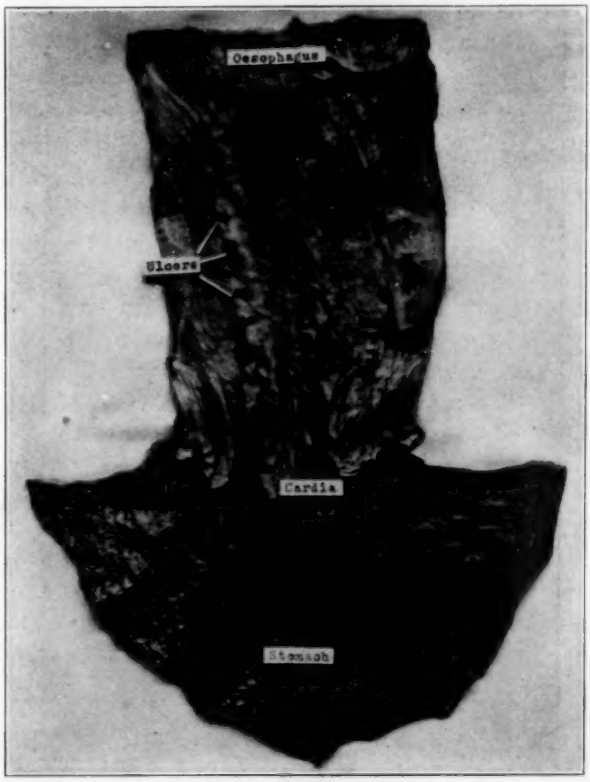


Fig. 6.—Multiple ulcers in the lower part of the esophagus along rows of varices in a case of portal cirrhosis with fatal gastro-intestinal hemorrhage.

and periesophageal regions with branches penetrating the muscular coat and uniting the two systems. If the mucosa is stripped off, the superficial set is found to lie in a series of rows in the long axis of the esophagus, gradually fading away above into the deeper set. On injection, the mucosa is elevated into ridges, the tips of which are especially susceptible to trauma, with consequent ulceration or rupture (fig. 6). Both groups are drained by the diaphragmatic, intercostal and azygos minor veins. The main source of supply is the coronary vein of the stomach. This branch which normally drains the lesser curvature and

cardiac end of the stomach opens into the trunk of the portal vein by turning down from the esophageal region and running to the right within the gastrohepatic omentum. When the collateral circulation is established in portal cirrhosis the blood current in this vessel is reversed and the veins along the lesser curvature become notably enlarged and varicose. It is practically only at the cardia, however, that the perforating submucosal veins become prominent. The factors favoring the formation of the esophageal varices are many. The proximity to the seat of obstruction and the comparative directness of the course no doubt are conducive to this as a site for an anastomotic pathway over others. The lack of support offered by the submucosal tissue to the veins in this situation, together with the constant movement to which they are subjected and the aspirating effect of the negative intrathoracic pressure, no doubt are responsible for their dilatation. In any event, of all the extraneous vascular channels developed as a result of portal obstruction and portal venous hypertension, this group alone is a course of considerable danger to the patient because of the frequent association of gastro-intestinal hemorrhage with it.

METHODS OF TREATMENT

By means of merbaphen and ammonium chloride, the dangers incident to ascites, itself probably an expression of portal hypertension and insufficient collateral circulation, have been greatly reduced. The consequent prolongation of life thus allows lesions of the vascular system to loom so large as to be responsible for about 50 per cent of the deaths in cases of portal cirrhosis. Of such lesions by far the most frequent and serious is gastro-intestinal hemorrhage from esophageal varices. In the light of the essential lesions of these vascular changes, it becomes important to consider how the integrity of the vascular system can be maintained without adding to the grave injury already suffered by the liver. The measures fall naturally into two groups, medical and surgical.

Medical Measures.—Within the field of the medical measures come all proceedings directed toward protecting the varices from trauma. A bland, soft, nonirritating diet without extremes of temperature, the avoidance of the use of the stomach tube and of everything which might induce vomiting and a minimum of exertion in order not to raise blood pressure are indicated. Following hemorrhage, however slight, there should be a period of complete rest to allow healing of the ruptured vessel, for the first rupture possibly predisposes to a second. In short, the same treatment should be employed as for a bleeding gastric or duodenal ulcer.

Surgical Measures.—In accordance with the underlying pathologic principles, surgical treatment may be directed toward removing or

destroying the bleeding varix, reducing so far as possible the amount of blood entering the portal circulation or increasing the collateral channels to such an extent that the portal hypertension and stasis will be relieved. While the first is not altogether a surgical impossibility, it would be a decidedly dangerous procedure. Cauterization of the varices through the esophagoscope is the only method by which it has been attempted, and so far this has met with little success. Another method of attack would be to ligate the coronary vein or group of veins between the cardia and the trunk of the portal vein, but the feasibility of this procedure is open to question. The second possibility, that of reducing the amount of blood entering the portal circulation, involves removal of the spleen, which contributes about 20 per cent of the total portal stream. This has already given good results in selected cases.

The most popular method of effecting an increase in collateral circulation has been the Talma-Morison operation with its modifications, such as the production of adhesions between various abdominal organs and the abdominal wall. All of them rely for success on the slow development of new anastomotic vessels in the adhesions so formed, and for this reason are open to criticism. The adhesions may never form, or the vascular pathways may be entirely inadequate. Moreover, the time required for their production may be much too long for the patient to derive any benefit from them.

Considering that the whole tendency of portal cirrhosis is to divert the stream of portal blood away from the liver, leaving the arterial blood to provide for the parenchymal requirements, the most logical and effective method of dealing radically with the embarrassed portal circulation would doubtless be to perform a simple Eck fistula. By this means the portal hypertension would be relieved, stasis immediately abolished, and the development of varices arrested. The ideal procedure would be side-to-side anastomosis of the portal vein and inferior vena cava without ligating any trunks. This would not interfere with any other blood already reaching the liver. Although Eck fistulas have been tried at various times, the resultant uniform failure seems to be entirely due to difficulties in the operation itself. Provided a satisfactory technic can be evolved, such as that employed by Mann and his associates in their experimental work with Eck fistula on dogs, there is no reason why in suitable cases it should not be successful.

COMMENT

To review briefly the outstanding points in the pathologic changes of portal cirrhosis as they affect the vascular system and the parenchyma is to trace a well ordered and steadily advancing sequence of events.

As a combination of destruction and regeneration of the parenchyma slowly progresses over a long period of years, there is a tendency toward a divorce of the hepatic cells from their supply of portal blood, a process which may be practically complete long before any evidence of hepatic insufficiency appears. The continuance of the apparently normal metabolism is due to persistence of the arterial supply to the parenchyma even though the portal supply has been reduced to a minimum. It is well known that when the liver is normal the hepatic artery is capable of bringing sufficient pre-urea bodies to the organ to maintain a normal excretion of urea in the entire absence of the portal vein, provided the circulation is not further embarrassed by a cardiac lesion or by venous stasis in the inferior vena cava (Doyon and Dufourt [21]). There comes a time, however, in cirrhosis when even this mechanism fails, and the arterial blood supply to the parenchyma is so reduced that signs of insufficiency appear. The condition of hepatic insufficiency in cirrhosis is therefore an expression of vascular deficiency rather than of deficiency of the liver cell.

While these alterative parenchymal lesions are taking place, the whole hepatic vascular system is slowly being merged with the connective tissue peripheral to the cell masses. Within this scar tissue, for it is nothing else, the natural slow progress toward avascularity obliterates primarily the portohepatic venous sinusoids and fine radicles, and leaves the arterial twigs for the time being. It is principally this venous obstruction which calls forth the slow development of the collateral anastomoses necessary for the diversion of the portal blood into the caval circulation. When the collateral circulation is fully established, the intrahepatic portal venous block is probably complete, and the amount of portal blood reaching the hepatic cells is practically reduced to zero.

The duration of the period from the time of the complete diversion of the portal current into its collateral channels to the obliteration of the persisting arterial blood supply of the remaining secretory tissue is longer or shorter according to the rate of sclerosis of the intrahepatic vascular bed and the varying degree of involvement of the two circuits. This dissociation of the portal venous and hepatic arterial blood circuits provides a rational explanation of many interesting clinical phenomena. Although the influence of biologic changes in the hepatic cells cannot be disregarded in the development of ascites, purely physical and mechanical factors are of the greatest importance. As an expression of the lack of balance occurring between the steadily progressive portal obstruction

21. Doyon, and Dufourt: Contribution à l'étude de la fonction uréoporétique du foie. Effets de la ligature de l'artère hépatique et de celle de la veine porte. Arch. de physiol. norm. et path. **10**:522, 1898.

and the rate of formation of the compensatory collateral circulation, one may better understand the mechanism of the occasional sudden onset of ascites, its transient nature or fluctuations in its amount. Ascites with its associated evidences of portal stasis is, per se, related only to the portal vein and is not necessarily an event of the gravest import since it affords no indication, except in a general way, of the extent of the reduction in hepatic reserve. Much may be done both medically and surgically during this period to relieve the ascites and to protect the patient against intercurrent conditions. When, however, signs of hepatic insufficiency appear, as shown by increasing retention of dye (in the absence of jaundice) it is clear that serious encroachment on the arterial supply of the nodules of hepatic tissue is taking place and that the last line of defense is in danger. Increasing retention of dye with ascites is therefore of much greater prognostic significance, and under such circumstances surgical treatment directed toward opening up new collateral channels would be ineffective.

SUMMARY

The changes that occur in the portal circulation and particularly in the intrahepatic vascular system as a result of portal cirrhosis are demonstrated by various means. An attempt is made to correlate the vascular alterations with those in the hepatic parenchyma, emphasis being laid on the physical and mechanical factors involved in the development of ascites. Progressive dissociation of the portal venous and hepatic arterial circuits is found of such a nature that the portal blood is diverted to collateral channels at an earlier stage of the disease than the arterial blood. The hepatic cells are thus divorced from their normal portal blood supply and are ultimately nourished almost entirely by the hepatic artery. Ascites is considered to be associated with a lack of balance between the progressive sclerosis of the intrahepatic portal radicles and the rate of development of the collateral pathways, while hepatic insufficiency is more closely related to the subsequent obliteration of the persistent arterial connections. The duration of the period between the completion of the two processes depends on the rate of intrahepatic sclerosis and is of great importance in treatment. Ascites, per se, is amenable to medical and surgical treatment but when complicated with signs of hepatic insufficiency, as evidenced by retention of dye in the absence of jaundice, it is of much graver import. It is an indication that the remaining arterial supply of the hepatic cells has been seriously reduced. The possibilities of various forms of treatment is discussed, with particular regard to bleeding esophageal varices.

ABSTRACT OF DISCUSSION

DR. NORMAL M. KEITH, Rochester, Minn.: This work of Dr. McIndoe and Dr. Counseller is exceedingly important and has thrown a great deal of light on some of the problems in chronic cirrhosis of the liver. One of the points in this disease that has been particularly interesting is that when there is marked ascites one can often empty the abdomen of this fluid by the use of diuretics. Dr. McIndoe has clearly pointed out that the portal circulation is practically non-working in these cases. How can this ascitic fluid be absorbed and secreted through the kidney? We feel from this work that it is impossible to change this severely injured portal circulation, that there must be some effect on the remaining liver cell. That brings up a point which is of interest in regard to the action of diuretics. It is almost impossible to believe that such an effect is solely on the kidney. The abdominal cavity is full of fluid, the kidneys are working normally, and yet that fluid is not being secreted. Give the patient a diuretic, and somehow or other that fluid is allowed to escape.

The experimental work done by Bolton of London is often forgotten. In 1916, he pointed out that by partially obstructing the vena cava above the diaphragm one could produce marked ascites, but if the animal that was used for the experiment was not treated for several weeks, this ascites was gradually reabsorbed. By injecting a dye into the ascitic fluid when its absorption was taking place, he showed that the absorption was through the blood vessels rather than through the lymphatics. In other words, the dye quickly appeared in the general circulation, in a much shorter period than it appeared in the lymphatic duct. I do not know whether such a mechanism applies in these cases after diuretics.

A further point of great interest in regard to this work is the question of the causation of extensive cirrhosis. I have seen cases, some of those that Dr. McIndoe studied, in which the clinical course has been that of syphilitic cirrhosis; but the terminal picture was that of a cirrhosis of Laennec. I have seen patients with a long history of disease of the gallbladder and cholecystitis and ascites. Death followed and the symptoms were those of a portal cirrhosis of Laennec. These must be different causes of this terminal condition and I think this work has emphasized that important fact.

DR. J. SHELTON HORSLEY, Richmond, Va.: Dr. McIndoe's demonstration of the vascular supply to the liver in advanced cases of cirrhosis gives a new point of view. That the portal circulation to the liver is not essential, and that the hepatic artery can take on the chief function of the portal venous circulation, is an interesting observation. His explanation that the arterial blood in the hepatic artery can be forced through the remaining hepatic cells and so have the pre-urea bodies removed, explains a phenomenon that was otherwise difficult to account for, and shows how a small proportion of hepatic cells, even though not reached by the portal venous radicles, may carry on an essential function of the liver for a long time. I fear, however, that he is somewhat too enthusiastic about the beneficial results of an Eck fistula in these cases. Carrel and others have made an Eck fistula in human beings for cirrhosis, but without satisfactory results. When the blood of the portal circulation is gradually diverted, as through the slowly-forming anastomoses that occur after the Talma-Morison operation, the body can adjust itself to such a change, but when the whole portal circulation is quickly shunted to the vena cava, the body is not prepared to deal with the overwhelming new products that are suddenly thrown into the general venous circulation. It is another illustration of a general biologic principle that a gradual change in function may sometimes be endured when a sudden change might be disastrous. In like manner the sudden deprivation of three fourths of the substance of the normal kidney would probably result fatally, though if this were taken away gradually but little ill effect would be observed. One among the many interesting points Dr. McIndoe brought out is that ascites is always accompanied by a dilatation of anastomotic veins, either anterior or posterior. If there seemed to be great urgency, it might be possible to anastomose one of these enlarged veins in the abdominal wall to one of the veins in the omentum. This

would give a more rapid emptying of the portal circulation than could occur after the Talma-Morison operation, but at the same time it would not convey all of the portal blood as would occur after the Eck fistula.

DR. A. H. MCINDOE: As far as the Eck fistula is concerned, I offer it only as a suggestion. The Eck fistulas performed in this condition by Widal, Rosenstein and De Martel were fatal, probably as a result of infection. I think the technic has a great deal to do with the success of the operation, and probably, as Dr. Horsley says, any anastomosis would be satisfactory. The important thing is that the trunk of the portal vein above the fistula should not be ligated at the time of the operation, so that any blood reaching the liver should not be prevented from still doing so. An Eck fistula can be performed in normal dogs with ease, and in addition 60 per cent of the liver can be removed without much change in the metabolism. These dogs live for as long as eighteen months. Perhaps the sudden switching of the portal circulation into the vena cava in cirrhosis would be too much, but it would require some experimental work to determine this point definitely.

SIXTY-THREE DEATHS FROM CARBON MONOXIDE POISONING IN PRIVATE GARAGES

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The number of deaths caused by the inhalation of carbon monoxide from automobile exhausts in closed garages is increasing. Every day during the winter months, the lay press contains reference to deaths in garages in some part of the country. During the last six years sixty-three deaths have occurred in Cook County (Chicago) alone. In private garages death from carbon monoxide is absolutely preventable, if people will open the doors and windows of the garage when the engine is allowed to run while they are warming up the motor or working on the car.

Early reports of death or poisoning from gas engines referred to "gasoline fumes" or "petromortis." Only after pathologic and chemical investigations was the true cause of death determined, for the post-mortem appearance and chemical proof of carbon monoxide poisoning was well known long before the advent of the automobile.

Longhurst [1] reported a death from petrol poisoning. Blumenshen [2] reported four deaths from automobile fumes. Johnson [3] reported forty-two poisonings, but no deaths, from fumes of a gasoline engine in a sewer. Harbitz [4] reported a death from carbon monoxide from the exhaust in a motor boat. Foote [5] reported three poisonings, but no deaths, in the hold of a submarine. McNally [6] reported that the exhaust gases of automobiles, as a source of poisoning, contained from 1.16 to 6.62 per cent carbon monoxide.

Briggs [7] repored the illness of two men and one death from the exhaust of a motor boat pouring into a cabin; the estimated time of exposure was fifteen minutes. Barclay [8] also reported deaths from carbon monoxide on a motor launch. Holmes [9] reported the death of a

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1. Longhurst: J. Royal Army Med. Corps **13**:584, 1909.
2. Blumenshen: M. Rec. **93**:342, 1918.
3. Johnson, J. W.: Canad. M. A. J. **3**:118, 1913.
4. Harbitz: Norsk. Mag. f. Laegevidensk. **15**:462, 1917.
5. Foote: U. S. Nav. M. Bull. **10**:681, 1916.
6. McNally, W. D.: Carbon Monoxide Poisoning, J. A. M. A. **69**:1586 (Nov. 10) 1917.
7. Briggs, J. E.: Gangrene Following Carbon Monoxide Poisoning, J. A. M. A. **73**:678 (Aug. 30) 1919.
8. Barclay: New Zealand M. J. **7**:42-46, 1909.
9. Holmes: Brit. M. J. **1**:812, 1925.

medical friend in a garage. Homan [10] reported the illness of twenty persons in a closed auto truck [11] twenty minutes after the car was started. Twelve men, found unconscious, were laid out on the road, and an effort was made to revive them. After ten minutes, eleven had recovered consciousness. A boy, aged 17, died. Two people seated near an engine in an excursion boat [12] were killed by the exhaust. Hitchcock [13] reported three fatal cases of poisoning in a garage and a fourth with a slow recovery: "After fourteen months of the accident an anterograde amnesia was still present, some emotional disturbance and some depression." Emerson [14] reported the illness and recovery of three children who entered a garage in a basement where the engine of a car had been running for ten minutes. Logan [15] reported carbon monoxide poisoning from the exhausts in closed motor vehicles, such as cars, lories and ambulances used at the front in the World War. Logan briefly alludes to the death of men returning in ambulances from the front in the English, French and Italian Armies. Reference is also made to a case in England and one in the Transvaal in which an intoxicated man fell

TABLE 1.—*Cubic Feet of Carbon Monoxide Liberated Per Hour*

Engine Speed	5-Passenger Automobile	7-Passenger Automobile	Light Trucks Up to 1.5 Tons
Idling	35	33	31
Racing	65	105	68

down behind a car near the exhaust and was killed by the carbon monoxide. Homan reported two cases in which persons were poisoned from fumes while riding in a closed car.[10] Ciampolini,[16] Kranenburg,[17] Henderson,[18] Yant,[19] and Hayhurst [20] report the dangers of exhaust gases from automobiles.

Fieldner [21] gives the amount of carbon monoxide liberated by engines of the various types divided into three classes.

10. Homan: Lancet **1**:1334, 1920.
11. Carbon Monoxide and Automobiles, Belgian letter, J. A. M. A. **83**:284 (July 26) 1924.
12. Brit. M. J. **1**:338, 1924.
13. Hitchcock, C. W.: Carbon Monoxide Poisoning, J. A. M. A. **71**:257 (July 27) 1918.
14. Emerson, P. W.: Carbon Monoxide Asphyxiation from Motor Exhausts, J. A. M. A. **82**:227 (Jan. 19) 1924.
15. Logan: J. State Med. **28**:306, 1920.
16. Ciampolini: J. Indust. Hyg. **6**:102, 1924.
17. Kranenburg: Nederl. Tijdschr. v. Geneesk. **78**:1794, 1924; **79**:509, 1925.
18. Henderson: M. Progress **40**:332, 1924.
19. Yant: J. Indust. & Engin. Chem. **16**:1047, 1924.
20. Hayhurst: Am. J. Pub. Health **16**:218, 1926.
21. Fieldner: Rep. N. Y. Bridge and Tunnel Commission, 1921, p. 91.

Yant, Jacobs and Berger [22] give the percentages of carbon monoxide in the air of a closed garage of 2,950 cubic feet capacity in which a five passenger car was running at 200 revolutions per minute. In twenty-five minutes the air contained 1.31 per cent, in sixty minutes, 2.10 per cent.

Kranenberg [17] investigated 157 public garages and found 0.10 per cent carbon monoxide in the air 10 feet from the exhaust of running motors, while at a distance of 30 feet he found none. In garages in which the air was contaminated to the extent of 0.2 per cent, almost all of the workers complained of headache. Forty workers from thirty-one different garages submitted to blood tests, and in 69.5 per cent of these carbon monoxide hemoglobin was found. Hood and Kudlich [23] reported that the exhaust gases examined by them contained carbon monoxide from a fraction of 1 per cent to 13.7 per cent.[24]

TABLE 2.—*Deaths in Chicago Due to Automobile Gas (Carbon Monoxide Poisoning)*

	Accidental	Undetermined	Total
1919	3	0	3
1920	3	0	3
1921	3	0	3
1922	1	2	3
1923	2	0	2
1924	11	0	11
1925	19	2	21
1926	17	0	17
Total	59	4	63

The majority of the cases contained in this report concern persons who were found dead in privately owned garages. One died after removal from a public garage. Fifty-nine of the deaths were accidental and four were undetermined as to whether accidental or homicidal; fifty-one, or 80.95 per cent, of the patients had insurance ranging from $200 to $100,000; over half of the policies were for $3,000 or less, three were for $5,000, one was for $6,000, one was for $34,000 and one for $100,000. Eleven, or 17.46 per cent of the persons were repairing their cars, while the others were found sitting at the wheel with the engine running. The records during June and July fail to show deaths in garages from carbon monoxide.

Carbon monoxide, when pure, is nearly insoluble in water, and is a colorless, tasteless and practically odorless gas. The lack of odor makes

22. Yant, Jacobs and Berger: J. Indust. & Engin. Chem. **16**:1047, 1924.

23. Kudlich: Bull. Dept. Interior, Bureau of Mines, no. 74, 1916.

24. Burnham: J. M. Hyg. **7**:254, 1925. Shumway: M. J. & Record **121**:657, 1925. Henderson and Haggard: Am. Pub. Health Rep. **36**:2215, 1921.

it extremely dangerous as a source of accidental poisoning. As this gas appears in the exhaust of gas engines, it is accompanied by carbon dioxide, oxygen, oil and unburned gasoline.

As carbon monoxide does not cause irritation of the air passages and is not noted by the sense of smell, it is respired freely, uniting with the red pigment of the blood corpuscles and forming a definite compound, carbon monoxide hemoglobin, which replaces the oxygen volume for volume. Occasionally, the exhaust gases are irritating because of the substances other than carbon monoxide, and a further warning is usually given by the light blue smoke that soon fills the garage. Exposure to a contaminated atmosphere for two or three minutes may cause serious illness. I entered a smoke filled garage, in which an engine had been running for ten minutes, remained for two minutes, with one small door open, and had a severe headache and nausea for four and one-half hours afterward.

The amount of carbon monoxide in the exhaust of gas engines varies, and in closed garages the onset of symptoms and time of death would also vary, depending on the percentage of carbon monoxide in the exhaust gas from the automobile. People rescued from garages before the onset of coma complained of giddiness, headache, vomiting and loss of muscular power. Loss of memory, convulsions and unconsciousness may follow, if treatment is not instituted promptly.

Sayer and Yant [25] found that the number of symptoms decreases with the rate of saturation.

SYMPTOMS AND PERCENTAGE OF BLOOD SATURATION

1. No symptoms—from 0 to 10 per cent.

2. Tightness across forehead; possibly slight headache, dilation of cutaneous blood vessels—from 10 to 20 per cent.

3. Headache, throbbing in temples—from 20 to 30 per cent.

4. Severe headache, weakness, dizziness, dimness of vision, nausea and vomiting, collapse—from 30 to 40 per cent.

5. Same as from 30 to 40 per cent, with possibility of collapse and syncope, increased respiration and pulse—from 40 to 50 per cent.

6. Syncope, increased respiration and pulse, coma with intermittent convulsions, Cheyne-Stoke's respiration—from 50 to 60 per cent.

7. Coma with intermittent convulsions, depressed heart action and respiration, possibly death—from 60 to 70 per cent.

8. Weak pulse and slowed respiration, respiratory failure and death —from 70 to 80 per cent.

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25. Sayer and Yant: Bureau of Mines, Report of Investigations, no. 2304, 1923, p. 5.

TREATMENT

Since the combination of carbon monoxide with the hemoglobin of the blood is not permanent, but relatively stable, and is gradually supplanted by pure air or oxygen, it is of the utmost importance to remove the patient to the air. Grehant [26] found that respiration of pure oxygen eliminated carbon monoxide four times as fast as when atmospheric air was breathed. Haggard and Henderson [27] recommended the use of 5 per cent of carbon dioxide. Other investigations have proved that the use of oxygen alone is satisfactory, and that it eliminates certain dangers which are to be feared in the administration of carbon dioxide by laymen. Therefore, the carbon dioxide-oxygen treatment is little used.

If the breathing is weak and intermittent, artificial respiration by the Schaefer method should be induced until normal breathing is resumed. The body should be kept warm by blankets, electric pads or hot water bottles, and stimulants should be administered to tide the patient over the period of low vitality. Hypodermics of caffein and sodium benzoate can be given. The patient should be kept at rest, preferably in a hospital, where the after-effects of the carbon monoxide can be treated symptomatically.

POSTMORTEM EXAMINATION

Poisoning by a small amount of exhaust gas may produce few changes, or, if the patient lives for a number of hours after removal from the garage in which the exposure occurred, only a careful examination of the blood will reveal the presence of the gas. The surface of the body is pink to red, more pronounced in the dependent parts. On opening the body the blood is cherry red, usually fluid, coagulating slowly. The pharynx, esophagus and stomach occasionally are reddened. Small hemorrhages are present in the pleura, with pulmonary edema and bright red froth in the air passages. The intestinal mucosa may also have small punctiform hemorrhages. All the tissues of the body are redder, owing to the presence of carbon monoxide hemoglobin. The hemorrhages found in the brain are never sufficient to cause compression. A characteristic change in prolonged exposure to carbon monoxide poisoning is the occurrence of punctiform hemorrhages and softening in the cortex and central nuclei of the brain, notably in the two internal segments of the lenticular nucleus. Lesions in the skin, following carbon monoxide poisoning from automobile

26. Grehant: Compt. rend. Acad. d. Sc. **132**:574, 1901.

27. Haggard, H. W., and Henderson, Y.: Treatment of Carbon Monoxide Poisoning, J. A. M. A. **77**:1065 (Oct. 1) 1921.

exhaust, are rare, probably because of the rapidity of death from a high concentration of carbon monoxide.

Haldane,[28] breathing air containing 0.12 per cent felt a slight palpitation of the heart in thirty-three minutes, and in ninety minutes his vision and hearing were distinctly affected. In two hours his vision and hearing were markedly impaired, and he experienced confusion of the mind and had a throbbing headache. From his experiment, Haldane concluded that 0.05 per cent of carbon monoxide in air is sufficient to produce symptoms in men and mice, and that a content of 0.2 per cent is distinctly dangerous to man.

SUMMARY

1. The number of deaths caused by the inhalation of exhaust gas of automobiles in closed garages is increasing.

2. A concentration of 2.0 per cent carbon monoxide can be easily obtained in a closed garage when the motor is running.

3. To inhale as much as 0.2 per cent of carbon monoxide is dangerous.

4. The action of the exhaust gas is due chiefly to the formation of carbon monoxide hemoglobin.

5. Carbon monoxide can be removed from the blood of the patient by replacing the carbon monoxide with oxygen of the air, pure oxygen or oxygen with 5 per cent carbon dioxide.

6. Deaths due to carbon monoxide in garages can be prevented by providing adequate ventilation, with the doors and windows wide open, when one is working on the car with the motor running, or by connecting the exhaust pipe to an outside vent.

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28. Haldane: J. Physiol. **18**:430, 1895.

Laboratory Methods and Technical Notes

SCOPOMETRY

A System for Optical Measurement and Study of Colloids and Other Dispersions *

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Dispersed systems are so common that practically all biologic materials at one time or another must be dealt with in the form of dispersions. Blood, milk, bacteria, etc., represent dispersions of everyday clinical interest, and immunologic phenomena such as agglutination, lysis and precipitation are important examples of colloidal reactions involving dispersed phases. In physiologic chemistry, dispersions of such frequently occurring substances as lipoids and proteins are of paramount interest, in that they hold the secrets of so many vital mechanisms which are not understood because of the inadequacy of present methods of analysis and measurement.

In research, the technical difficulties of separating and measuring dispersed materials demand not only elaborate, laborious and lengthy chemical procedure but physical methods of extreme refinement and complexity such as ultramicroscopy, ultrafiltration, membrane potential and electrical conductivity measurements and cataphoresis, and optic methods like spectrophotometry, nephelometry and turbidimetry. Of these, only some of the optic methods are adapted to clinical use, because they alone offer the necessary convenience and rapidity.

Every dispersion is characterized by the visual effect of cloudiness or turbidity which may be so slight as to escape the unaided eye, or so dense as to seem opaque, even in thin layers. In whatever degree it may occur, however, cloudiness is an important property of every dispersion and has therefore engaged a great deal of scientific attention, principally in the fields of physics and chemistry. In chemistry, the nephelometer and Duboscq colorimeter have been thoroughly tried for measuring the concentrations of dispersions by brightness in the same restricted way that colorimetry serves as a shortcut to concentration, and biologic literature shows numerous technics which have been devised for

* From the Laboratory of the Prudential Insurance Company.

* Read before the Section on Pathology and Physiology at the Seventy-Eighth Annual Session of the American Medical Association, Washington, D. C., May 20, 1927.

quantitative determinations with them. Undeniably, however, both methods have been generally abandoned as being too "tricky" and "unreliable." Thus, in describing a new sulphur technic, chemists state: "Although nephelometric methods are in general unpopular and subject to severe and just criticism, no other principle was found possible." Again, in a recent survey of turbidity methods, a physicist declares: "Every attack on dispersed systems is disappointing because of the baffling complexity of the phenomena. . . . No one (optic method) has yet been accepted as a standard. . . . Apparently turbidity methods have not proven satisfactory."

SCOPOMETRY

The present communication purposes to explain briefly several principles which seem to me to account for the failures of existing turbidity methods and to present new principles and methods which can be easily and quickly applied by means of a new optic instrument which I call the scopometer (*σκοπεῖν*—to view, and *μέτρον*—measure).

The explanation is also offered that interest in turbidity methods has been hitherto so closely confined to the practical advantages of quick chemical quantitation that the more fundamental considerations involved in relating the properties of dispersions to the complex but effective and delicate nature of light waves has been overlooked. In fact, the possibility of deriving qualitative as well as quantitative information concerning dispersions by measuring the same sample with various light effects seems never to have been appreciated.

If several concentrations of a dispersion are measured by more than one optic method and the results plotted, differences between the measurements appear which, on examination, prove definitely systematic for each type of measurement. Such observations, therefore, lend themselves to correlations which are found to indicate not only concentration but the size of particles and other structural features of dispersions. Moreover, by varying constants such as temperature, by testing the dilution law, by making observations at intervals after the incipience of reaction and by other treatments, it is possible to gain information about the formation and growth of particles and the velocity and mechanism of reactions. In passing, it may also be noted that scopometry offers new methods of colorimetry based on spectrometric principles which promise in conjunction with the other methods to yield a sufficient number of variants to make it feasible to classify dispersions.

EXISTING TURBIDITY METHODS

The effects of vapors on light concentrated at right angles to a glass tube containing them showed Tyndall [1] that the blue of the sky results

1. Tyndall, J.: Contributions to Molecular Physics and Proceedings of Royal Society, 1869, p. 108.

from polarization of light by particles fine enough to scatter light instead of to reflect it as they do when they are larger. Later, Richards,[2] looking for greater accuracy in determining molecular weights, constructed an instrument to compare the Tyndall effect of an unknown sample with that of a known standard prepared in exactly the same way and at the same time as the unknown sample. Richards' nephelometer has since been modified by Bloor,[3] Kober,[4] Marshall,[5] Kleinmann[6] and others, and in biochemistry nephelometry has been used almost to the exclusion of other turbidity methods. It is extremely sensitive, much more so than the balance, but optically it is the most complicated of all turbidity methods.

Folin[7] and others prefer the Duboscq colorimeter, which measures diffuse density by transmitted instead of reflected light. This seems to be the only form of turbidimetry that has found practical use in biochemistry. The literature on optics, however, is rich in instruments for measuring turbidity, and some of them are valuable in industrial technology. Besides turbidimeters, one finds cryptometers, diaphanometers, dispersimeters, densitometers, opacitimeters and tyndallmeters.

Tyndallmetry resulted from the effort of Richards' associate, R. C. Wells,[8] to improve nephelometry by substituting constant glass standards for the freshly prepared labile standards. This move in the right direction led to the development of tyndallmeters by P. V. Wells,[9] Mecklenburg and Valentiner,[10] Weinberg,[11] Vernes,[12] Tolman[13] and others, which measure the ratio of scattered or reflected light to incident light. The tyndallmeters seem to have been constructed for special researches,

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2. Richards, T. W.: Proc. Am. Acad. Arts & Sc. **30**:385, 1894.

3. Bloor, W. R.: J. Am. Chem. Soc. **36**:1300, 1914; J. Biol. Chem. **17**:377, 1914; **22**:145, 1915; **36**:33, 1918.

4. Kober, P. A.: J. Am. Chem. Soc. **35**:290 and 1585, 1913; J. Indust. & Engin. Chem. **10**:556, 1918.

5. Marshall, J. T. W., and Banks, H. W.: Proc. Am. Phil. Soc. **54**:176, 1915.

6. Kleinmann, H.: Biochem. Ztschr. **99**:19, 1919; Koloid-Ztschr. **27**:236, 1920; Biochem. Ztschr. **137**:144, 1923.

7. Folin, O.: J. Biol. Chem. **16**:289, 1913; **18**:263, 1914.

8. Wells, R. C.: Am. Chem. J. **35**:99, 108 and 508, 1906.

9. Wells, P. V.: Bur. Standards Sc., Paper 367, 1920; J. Am. Water Works A. **9**:488, 1922; Chem. Rev. **3**:331, 1927.

10. Mecklenburg and Valentiner: Ztschr. Instrumentenk. **34**:209, 1914; Physik. Ztschr. **15**:267, 1914.

11. Weinberg, A. A.: Biochem. Ztschr. **125**:292, 1921.

12. Vernes, Arthur: L'Organisation de la syphilimetrie, part 2, Paris, Malonie et Fils, 1923.

13. Tolman, R. C.: J. Am. Chem. Soc. **35**:317, 1913. Tolman, R. C., and Gerke et al.: J. Am. Chem. Soc. **41**:575, 1919.

because until recently (Vernes) none has found its way into biologic laboratories, although Tolman's has found application in the investigations of dust and smoke.

EXPERIENCE WITH EXISTING METHODS

In the course of a study of protein precipitans extending over several years, an intensive experience with nephelometers and Duboscq colorimeters, at that time the only available instruments, taught that turbidimetry is less sensitive to slight variations in precipitates than nephelometry, and that its law of dilution follows a simpler relation. Against these more complicated functions of the nephelometer, the turbidimeter has decidedly less range, especially at extreme dilutions, a defect of great practical importance, because it precludes measuring specimens of low concentration. Like all photometers, both methods are impaired by a difference in color between sample and standard, and both suffer from the same troubles inherent in the preparation and control of standards.

Richards rightly insisted that the standard not only should be of the identical material but should closely approximate the unknown sample in concentration. I found this impossible for many determinations, and tried, without success, various other suggestions found in the literature, including the single standards advocated by some workers. Patient experimentation along these lines finally led me to the conviction that except for a few special determinations, the troubles with fresh standards are insuperable and largely responsible for the failure of turbidity methods which employ them. Thus, each concentration of protein when precipitated follows a distinctive time law of turbidity growth which varies with the concentration not only of protein but of precipitant. Such differences in velocity directly conflict with the approved practice of reading all unknown samples at the same predetermined time, usually after ten minutes, because at such a time neither precipitation nor particle growth is complete, and differences in concentration or otherwise between standard and sample are emphasized by effects due to the difference in rates of the continuous changes going on in both.

These, with other considerations, led to a trial of tyndallmetry by substituting for fresh standards opal and other glasses on one side of the instruments. The results proved encouraging, but a more extended trial of tyndallmetry had to await the development of the scopometer, because at that time none of the tyndallmeters described in the literature could be located. Descriptions of Tolman's, Vernes' and Holker's [14] instruments appeared later.

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14. Holker, J.: Biochem. J. **15**:216, 1921.

THE EXTINCTION METHOD

Even the ancients saw objects vanish into the depths of the sea; and the disappearance of an image under observation is an accepted criterion in water and sewage analysis and in the manufacture of paints, photographic materials, etc. Evidently, the principle of extinction was

TABLE 1.—*Results with Crude Turbidimetric Methods in Determination of the Protein Content of Standard Serum Solutions and of Urine Showing Correspondence with Results by Other Methods*

1. Turbidimetric readings of protein content of standard solutions of serums and plasmas, prepared by dilution of known solution (200 mg. per 100 cc.)

Standard Set Number	Solution	Turbidimetric Estimates, Mg. per 100 Cc. Tubes 1	2	3	4	5	6	7	8	9	10	11
1, 2, 3 and 4	Sheep serum.....	100	80	60	50	40	30	25	20	15	10	5
5	Sheep serum diluted with normal urine	100	80	..	50	40	..	25	20	..	..	..
6	Sheep serum diluted with gum arabic..	100	80	60	50	40	30	25	20	15	10	..
7	Sheep plasma.....	100	80	60	50	40	30	25	20	15	10	5
8	Steer plasma											
9	Steer serum.....	100	80	60	50	40	30	25	20	15	10	..
10	Steer plasma diluted with 1% sodium chloride to 100 mg. protein concentration.....	100	80	60	50	40	30	25	20	15	10	5
11	Pig serum.....	90	70	..	45	..	35	25	20	..	9	..

2. Determination of protein content in 9 specimens of urine

Specimen Number	Mg. per 100 Cc. by Extinction Test (Exton) on Precipitates	Macro-Kjeldahl	Micro-Kjeldahl
1	190	185	196
2	350	322	333
3	110	115	115
4	20	16	18
5	44	40	41
6	50	53	52
7	70	64	67
8	45	40	47
9	70	75	71

3. Determination of protein content of serum and of urine

Solution	Mg. per 100 Cc. Gravimetric	Kjeldahl	Turbidity (Not Including Errors Due to Adsorption)
Serum: Total protein.....	54	55.7	57
Albumin.....	20.9	19.7	20
Globulin.....	38.2	35	35
Sum of fractions.	59.1	54.7	55
Urine (with serum added)	69.5	62	60

never applied to biologic materials, because the existing methods are too crude and demand impossibly large samples.

When experience with comparison methods convinced me that fresh standards were in reality integral parts of an instrument and that their satisfactory management was hopeless, the absolute freedom from troubles with standards offered by the principle of extinction became

immensely impressive, and attracted me to experiment with the possibility of contriving an extinction criterion of sufficient fineness for biologic technics. A crude method, first tried, consisted of measuring the height of a column of fluid that caused the disappearance of an image from its surrounding field. The results of such turbidimetric measurements of concentrations are compared with results by other methods in table 1. A similar test for sugar was also developed in which a complex but stable precipitate was obtained by the reduction of ferricyanide to ferrocyanide by the sugar, with subsequent precipitation with zinc in the presence of ammonia. Pure sugar solutions precipitated on different days during the period of experimentation gave a maximum difference of 6 per cent. Similar determinations of the sugar in fifteen specimens of urine deviated, on an average, less than 2 per cent from the readings by Sumner's colorimetric method.

Trials of different magnifications of many and varied objects adapted to the observation of the disappearance of an image from its surrounding field led to the adoption of a glass disk with a platinized circular middle portion and a transparent slit in its center. With this as a standard target, an instrument was constructed, in 1918, to view and register the depth at which the target disappeared with a 15 cc. sample. Since then, improvements in mechanical and optic design suggested by experience have been incorporated in more than a dozen successive models, and the later instruments gain in range and sensitiveness from hollow sphere integration effects, which give more perfect diffusion, by utilizing a tyndall beam in conjunction with transmitted light. Furthermore, an exceedingly important and distinctive compensation effect is achieved by the reciprocating changes of tyndall beam and transmitted light with changes in depth which yield a nearly pure measure of obstruction to the light rays forming the target image. The new method approximates simple proportionality closer, and is much freer from flocculation, light and color interferences than former methods.

THE SCOPOMETER

When observations made on the same sample both by the new extinction method and by the older photometric methods were compared, results which I had hitherto accepted as freaks or errors became so regular and striking as to make it unreasonable to so regard them, and search for a more reasonable explanation made it plain that the extinction method differs qualitatively from other methods and is, therefore, a new index of turbidity. It was naturally a matter of interest to correlate the results of a new measure with those obtained by older methods, and attempts to do this led to the discovery of a very important principle hidden in the complex composite nature of turbidity. A turbidity is

the resultant mass effect of many variables, some of which are preponderatingly sensitive and others relatively insensitive to a particular light effect. Consequently, each specified light effect, or different kind of measurement, is more specific for some structural variable of a dispersion than for others. This principle seems not to have been appreciated heretofore, but it is applicable to the analysis of dispersions and becomes obvious when correlation of the measurements made on the same dispersion by different optical methods is attempted (fig. 1).

The scopometer is an optic instrument designed to apply this principle easily and quickly. It provides a handy and efficient means for making many different kinds of measurements without disturbing the sample, and is unique in offering extinction and photometric criteria as well as polarization measurements in the same instrument (fig. 2). The diagram shows how the light source separates into three beams; the lower beam goes to a mirror which reflects it up through a cell holding the sample to form the inner field. The upper beam also goes to a mirror which deflects it through two nicol prisms, one of which can be rotated, to control the light forming the outer or comparison field of a photometric prism. The middle beam furnishes the tyndall beam. The cup holding the sample rests on the open grooved floor of the instrument, beneath which are slides for the quick changing of targets, stops or filters. On the side of the instrument are two thumb wheels; one changes and registers the depth of the sample by means of an optic plunger and scale, while the other opens and closes the slot which admits the tyndall beam. It will also be noted that absorption and turbid wedges are provided for both photometric fields.

By these means measurements can be made by changing the thickness of the layer examined or at a constant depth which makes practicable the measurement of gels, solid materials, smokes, etc. Thus, three different measurements by tyndall beam, two by transmitted light and two by extinction are provided, and each can be made at a given depth, at a given color absorption or at a given wedge position. One of the most interesting features of scopometry is the provision for measuring separately the polarizing and depolarizing effects of dispersions on the tyndall beam by means of a nicol prism with a scale placed in its path, and the vertical and horizontal components of the polarized light are now being investigated in the Prudential Insurance Company's laboratory. The range of the scopometer runs practically all the way from distilled water to opacity. The tyndall beam methods are most sensitive at extremely high dilutions, and the extinction method at high concentrations. In practice the instrument has proved remarkably stable, the change of lamps, etc., being possible without necessitating a change of calibration.

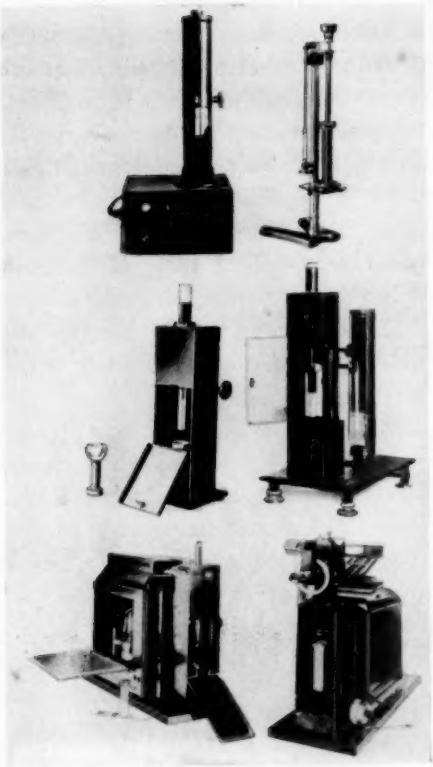

Fig. 1.—Some experimental models of the scopometer.

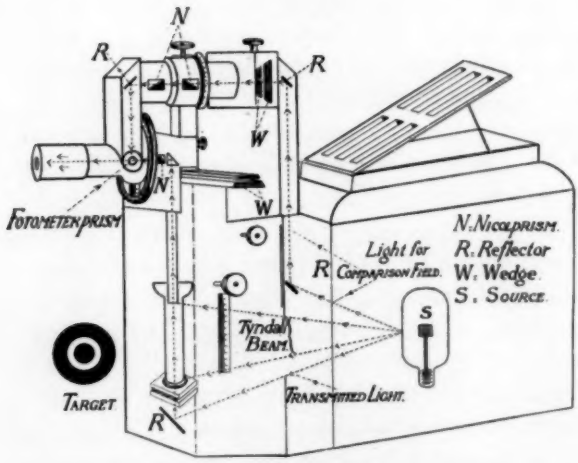

Fig. 2.—Diagram of the scopometer.

REPRODUCIBILITY OF DISPERSIONS

The rapidity of quantitation and the ability to make determinations that are impossible by other technics have hitherto monopolized interest in turbidity methods, to the exclusion of other probably more important advantages. The confessedly disappointing results have been blamed on both instruments and dispersions, some workers going so far as to claim that dispersions cannot be reproduced. The existing optic methods are, in my opinion, good but insufficient, and the results with different types of dispersions studied in the Prudential Insurance Company's laboratory have in each case demonstrated a reproducibility satisfactory for all clinical purposes.

A close analysis of the scant data on reproducibility in the literature agrees with my experience, although the casual reader might gather a conflicting impression. Thus, Kober and Kleinmann, both inventors of nephelometers, failed to reproduce satisfactorily silver chloride suspensions, while Boutaric,[15] Lamb [16] and others succeeded, and the reproducibility of photographic emulsions is, of course, well known. It is indisputable that some technics do not give as good reproducibility as others, but this happens because many of them stress secondary instead of first order effects. A few fundamental considerations help make this distinction clear.

The visual effect or optical quality of a turbidity depends on many different elements which contribute to it, especially the number, size, shape, color and transparency of the particles, and the refractive index of particles relative to medium. Thanks to studies of fogs, etc., by Barus,[17] Wilson [18] and others and the mechanism of precipitation by von Wienmarn [19] and others, it is known that condensation, and probably precipitation, phenomena occur in zones, some of which are relatively stable and others critical in the sense that slight changes occurring in them cause the precipitation of different orders of nuclei producing different sizes and numbers of particles. It is therefore of prime importance that a technic should provide for precipitation in a stable zone of supersaturation. By way of illustration, the proteins of blood and urine give reproducible results when precipitated with an equal volume of 5 per cent sulphosalicylic acid loaded with sodium sulphate, but when treated with larger volumes of weaker acid a third or more of the results go wrong (table 2).

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15. Boutaric, A.: J. de chim. phys. **12**:517, 1914; Ann. phys. **9**:113, 1918; **10**:5, 1918; J. phys. **9**:239, 1920.

16. Lamb, Carleton and Meldrum: J. Am. Chem. Soc. **42**:251, 1920.

17. Barus, C.: Physiol. Rev. **22**:82, 1906.

18. Wilson, C. T. R.: Smithsonian Report for 1904, p. 195.

19. Von Weinmarn, P. P.: Washburn Physical Chemistry, ed. 2, 1921, p. 432; Chem. Rev. **2**:217, 1925.

Another first order effect is the time element, which is hopeless with fresh standards but which does not cause any difficulties when conditions are known. If the turbidities of different concentrations of the same protein are measured at intervals after the incipience of precipitation, it is seen not only that they vary with concentration, but that the turbidities increase at a different rate for each concentration; also that after they have reached a maximum, little change in turbidity is apparent. This state of equilibrium, while not complete in a thermodynamic sense, seems to occur with all precipitates and is a favorable time for making optic measurements. Thus, sulphosalicylic acid protein precipitates (fig. 3) can be brought into suspension by turning of the test tube even after they have settled, and in reproducibility experiments I do not hesitate to precipitate one day and to make the reading the next. Some

TABLE 2.—*Comparison of Determinations of Protein Content Obtained by Supersaturation with Sulphosalicylic Acid and Sodium Sulphate with Those Obtained with a More Dilute Acid Solution in Larger Quantities*

Method	Results with 13 Specimens: Mg. per 100 Cc.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Supersaturation: precipitation with equal volume of 5 per cent sulphosalicylic acid, with sodium sulphate													
Gravimetric	72	25	55	21	55	31	50	50	64	62	120	336	113
Exton	75	30	50	25	50	20	40	40	50	50	120	300	125
Precipitation of 1 part urine with 24 parts of 2 per cent sulphosalicylic acid	200	75	100	75	150	200	200	100	100	100	200	1000	200

precipitates have less latitude, while others, like that of Rose's sugar test, can be read immediately after precipitation or at any time during the day. While it does not occasion any technical difficulty, the time element must be definitely known, and data concerning the velocity of a reaction must be included in descriptions of technic.

Temperature affects turbidity, but probably not any more than it does color. It is easily controlled, and while most of my work has been done at room temperature, there are instances in which the heating of solutions before precipitation and the use of thermostats will be advantageous. Like temperature, surface tension can also be utilized in devising satisfactory technics, and, of course, p_H is always important. In short, the choice of method and the physical details are most important in the technic of reproducibility.

Many precipitates change in appearance when they are violently agitated, but violence is never necessary, and gentle turning of the test tube usually suffices to restore a suspension. A study of protein precipitation (table 3) shows that even when it is shaken violently the effects

are of a secondary order and usually negligible. The precipitant invariably should be in excess, and the proper order and rate of mixing the solution and the precipitant must be determined and specified for each kind of analysis, and then be uniformly carried out when the tests are made.

If the conditions which have been outlined are incorporated in precipitation technics, reproducibility should follow, unless some inadvertent deviation from the established technic occurs or some contamination or unexpected foreign substance is present which interferes with the test.

Undoubtedly, much of the distrust of existing turbidity methods is due to wrong results caused by complications, against which the worker

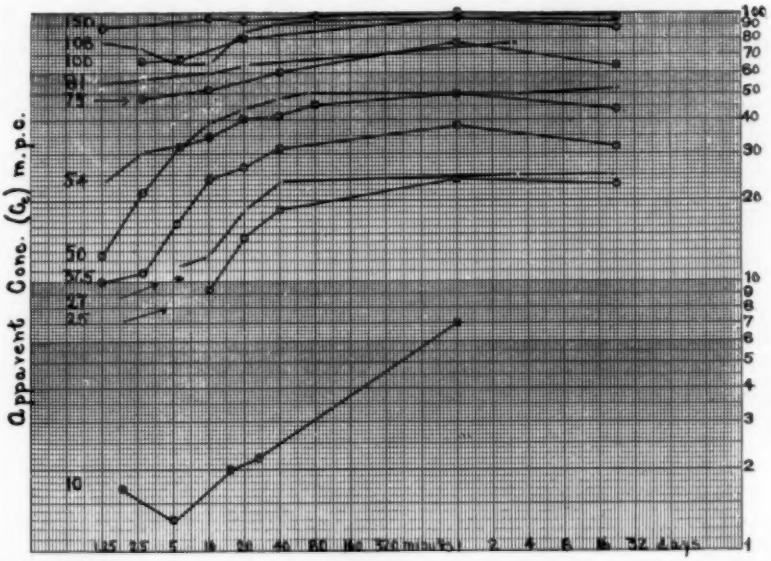


Fig. 3.—The increase in turbidity of precipitated protein dispersions (ordinate) according to the time (abscissa), showing increased rate of growth of turbidity, with increased concentration, and stability of precipitates when the maximum turbidities are attained.

could not protect himself, because he did not have any means of knowing they were operative. It is now possible, however, to avoid being misled and to know whether a test runs true by merely measuring precipitates with more than one of the several optic methods available with the scopometer. Thus, semen, protamines, peptized proteins, resins, etc., in urine, yield precipitates which cannot be distinguished from albumin clouds by any single optic method; but their presence is immediately detected and the possibility of error eliminated by scopometry, as happens, for instance, with specimens of urine which show apparently similar clouds when treated with sulphosalicylic acid (table 4).

APPLICATIONS OF SCOPOMETRY

Turbidity methods have already been applied to technologic and biochemical technics too numerous to mention here, but owing to their inconsistencies the existing turbidity methods have been generally abandoned in favor of colorimetry, titration or other lengthier technics, except for such determinations as are otherwise impracticable. With the

TABLE 3.—*Effect of Mixing Conditions on Protein Precipitates (Exton Test)* *

Conditions: Combination—Serum and Sulphosalicylic Acid		Age of Precipitate, Hours	Apparent Concentrations: Mg. per 100 Cc. Extinction C/e	Density C/d	Tyndall Polarized C_1	Beam Depolarized C_0	Turbidity Ratios C_e/C_d %	C_0/C_1 %
Shaken violently 1 minute	Serum added to acid	½	24.2	16.6	16.8	17.6	147	99
		24	26.7	19.5	18.7	20	137	94
	Acid added to serum	½	26.5	19.8	18.6	19	134	98
		24	28.4	21.5	19	20.4	132	93
Poured back and forth twice	Serum added to acid	½	21.8	24.1	24.3	24	90	101
		24	26.7	24	26	24.7	111	105
	Acid added to serum	½	22.0	24.5	26	24	90	108
		24	26.7	25	27	24.7	107	109
Left stratified, serum on top	Serum added to acid	½	25.8	25.6	25.4	24.8	110	103
		24	32.7	26.7	25.4	26	122	98
	Acid added to serum	½	26.8	26.8	26	26.6	100	96
		24	30.3	27.8	26	27.8	109	94

* Actual concentration of solution equals 25 mg. per hundred cubic centimeters.

TABLE 4.—*Comparison of Protein and Protamine Precipitates (Exton Test)*

Optic Method		Apparent Concentrations: Mg. per 100 Cc. Urine Containing Protein*	Protamine*
Extinction	(C_e)	25	25
Density	(C_d)	58	146
Polarized Tyndall	(C_1)	26	24
Depolarized Tyndall	(C_0)	26	22
Turbidity ratio (indicates particle size)	(C_e/C_d)	100%	40%
Probable average particle size		0.2 microns	0.08 microns
Corresponding number of particles		30 billion per cc.	500 billion per cc.

* Both precipitates are submicroscopic.

modifications necessary to adapt existing technics for scopometry, it should be possible not only to revive, but even to extend greatly, the usefulness of turbidity methods as short-cuts to concentration.

Usually, substances in complex mixtures or solutions are separated easily and quickly by precipitation, emulsification, saponification, and other processes in the form of dispersions which can be measured rapidly in the scopometer, a signal advantage over the time-consuming labors often involved in determinations by other means. Again, gravimetric

and other forms of analysis destroy the sample which is often not injured by turbidity methods and can therefore be used for other determinations. Moreover, scopometry is always a micromethod and never fails because of sample inadequacy, since it measures as little as even a few parts per million. Such practical advantages promise to bring within the realm of clinical application determinations which are now possible only in the biochemical laboratory.

In the Prudential Insurance Company's laboratory, scopometry has found practical application in the determination of total proteins and the protein fractions of blood and urine, sugar, chlorides, calcium, fats, soaps and other constituents in the analysis of blood, urine, milk and water, in

TABLE 5.—*Turbidity Ratios as Indicators of the Size of Particles for Various Dispersions*

Sample	Concentrations Mg. per 100 Cc.		Turbidity Ratios (Size of Particles)		Direct Classification of Size of Particles
	Actual	Apparent	C_e/C_d %	C_e/C_i %	
Horse serum (standard precipitate)	25	25	100	100	Just visible microscopically
Zinc oxide					
In glycerol	6.9	13	50	102	0.15
In water	6.9	6	42	98	0.15
	6.9	10	51	181	0.3 microns, averages by Dr. Green
In water	6.9	7	47	235	0.4
	6.9	3.7	64	357	0.7
	6.9	3.2	76	418	1.23
Gum benzoin in water					
Fractions: Top	..	3.1	54	59	Bluish white submicroscopic
Bottom	..	2.7	56	99	
Top	..	13.7	40	72	
Bottom	..	11.4	42	84	
Soluble starch	..	13	81	66	Had not settled in 3 months
Horse serum (sulphosalicylic acid precipitates)					
0.5 per cent acacia	25	9	41	85	Fine white precipitate
0.25 per cent acacia	25	17	61	100	
No acacia	25	24	77	112	Granular precipitate
Horse serum in ammonium sulphate					
Globulin	..	57	150	90	Fine white precipitate
Albumin	..	28	112	106	
Silica suspension	..	7	81	286	Coarse granular precipitate

the timing of hemolysis and in the counting of bacteria and blood cells. It has also proved an extremely quick and simple method for the determination of the solubilities of various salts of ferricyanide and ferrocyanide when one is establishing a choice of procedure for the quantitative separation of these anions.

Because turbidity methods seem to have been ignored by workers in fields other than that of chemical quantitation, it is necessary to point out that light vibrations have fundamental properties which offer possibilities of usefulness in the study of vital phenomena, and that the innovations incorporated in the scopometer may be regarded as constituting a new tool for their study and measurement. Thus, light waves have color and are subject to diffraction, refraction, reflection, diffusion, scattering, absorption, polarization, etc., by the mediums they traverse. All

of these effects are involved in scopometry, and variations among the values obtained with the scopometer, when properly correlated, denote structural characteristics of the dispersed material, such as the number, size, shape, color, etc., of the particles (table 5). Thus, suspensions of the same material made by different processes, such as the zinc oxide samples furnished by Dr. Henry Green, were measured, and the number and size of particles in each sample were determined by correlating the values obtained with the scopometer (fig. 4)—even when the particles were smaller than the wave length of light, and therefore beyond the

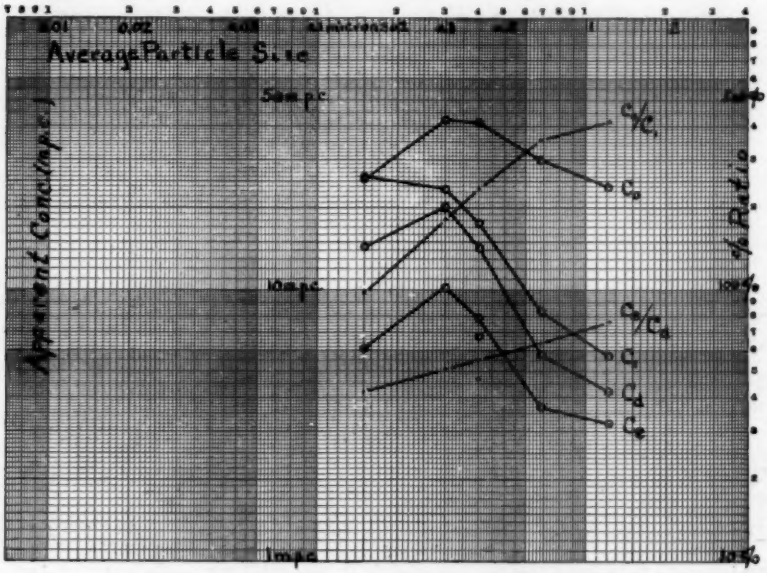


Fig. 4.—Relation of the apparent concentration of dispersions (ordinate) of zinc oxide in water, as determined by different optic methods, to the average size of the particles (abscissa). Actual concentration equals 6.94 mg. per hundred cubic centimeters; and size of particle equals determinations by Dr. Green. Concentrations were determined by extinction (C_e), by diffuse density (C_d) by polarized tyndall beam (C_1) and by depolarized tyndall beam (C_o). The ratios (in percentage), C_o/C_1 and C_e/C_d, indicate the derived sizes for the particles. The different apparent turbidity with different methods; the occurrence of maximum turbidity with different sizes of particles; the regular increase of ratios (C_e/C_d and C_o/C_1) indicating particle size, and the sensitiveness of polarized light (C_1) to smaller particle sizes and of extinction (C_e) to larger sizes should be noted.

resolving power of the microscope. In the same way, it is possible to determine the number and size of particles like blood cells and bacteria (figs. 5 and 6), and not being limited to the range of the microscope, scopometry may also serve to classify the ultra filters used in colloid chemistry and bacteriology.

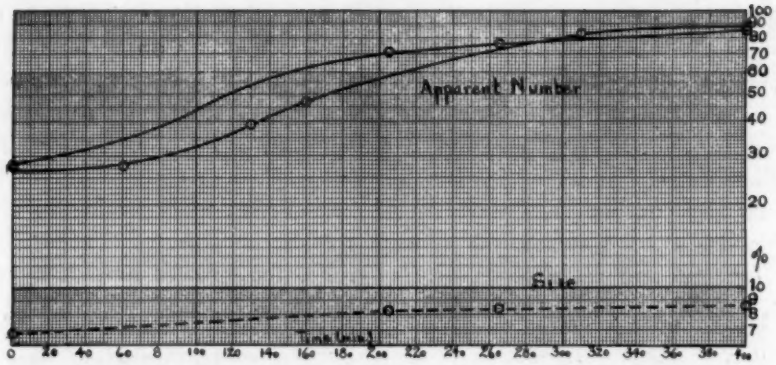


Fig. 5.—Rate of increase of apparent number of typhoid bacteria in peptone with a fairly constant curve for the size of particles (bacteria) as determined by the scopometer.

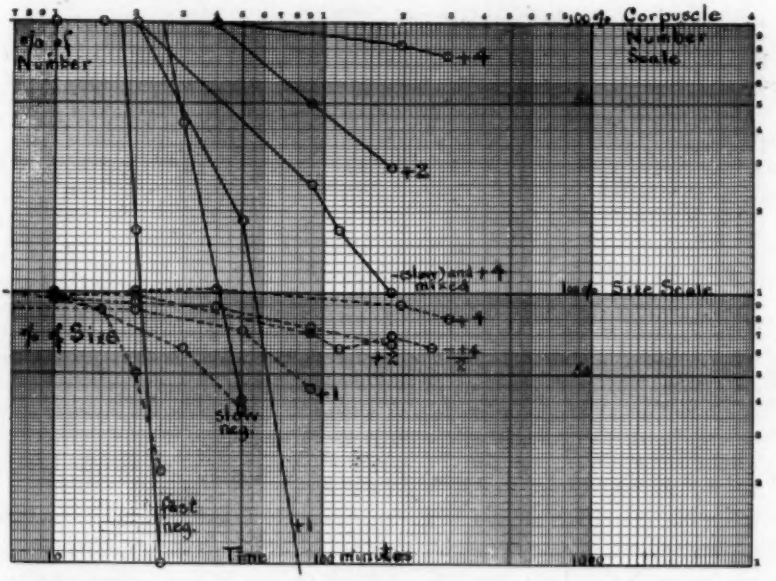


Fig. 6.—Study of hemolysis (Kolmer-Wassermann technic) with the scopometer, showing the rate of decrease in both the number and the size of the particles (red blood cells), with the slower change in size. The figures + 1, etc., at the ends of the curves indicate the readings of the routine tests.

Furthermore, light waves are peculiarly well suited to the study of biologic phenomena and can be used to measure them while they are taking place, because the mildness of their action permits them to traverse mediums in which vital processes are going on without disturbing the most delicate equilibria. Designed with a view to the study of mechanism as well as structure, the scopometer enables rapid and convenient shifts from one kind of measurement to another, so that the values obtained at intervals after the incipience of a reaction represent practically continuous observation of transformation occurring in colloidal and other dispersions. Thus, the order and rate of changes due to ferment and catalytic activity (fig. 7), the growth and decay of

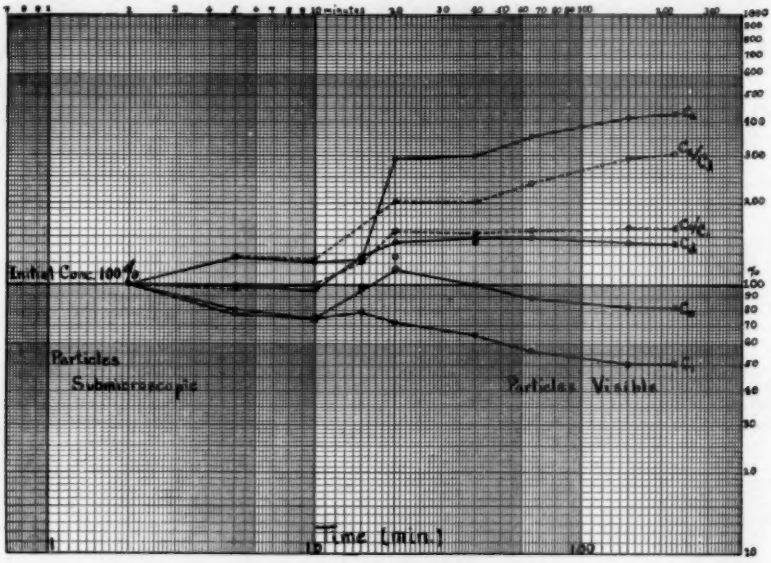


Fig. 7.—Study of enzyme action on soluble starch by readings by different optical methods with the scopometer, showing changes in the size of particles (C_e/C_a and C_e/C_1), with progress and apparent complexity of reaction, with indication of structural change in connection with hydrolysis.

micro-organisms, changes resulting from agglutination and lysis, such as bacteriophagy and hemolysis (fig. 6), and other serologic and immunologic phenomena, such as precipitation and flocculation, all of them being typical examples of transformations taking place in the dispersed phase, are susceptible to scopometric measurements, as are also all instances of changes from the continuous to the dispersed phase, or the reverse.

Interpretation of all the correlations involved in the various measurements must await further study and experiment, but from data already at hand it is evident that scopometry is to be regarded as a new system of analysis. The color effects of dispersions and colorimetry with the scopometer will be dealt with later.

SUMMARY

By means of a new instrument, the scopometer, measurements of dispersions can be easily and quickly made by several different optic methods without disturbing the sample. These include a measurement of diffuse density (turbidity), several of tyndall beam intensity (nephelometry, polarized and unpolarized) and new extinction methods for both turbidimetry and colorimetry based on correct spectrophotometric principles. The new extinction method estimates concentration more directly and with better reproducibility than previous turbidity methods.

Correlation of observations by the various methods available yields information about particle size and other structural characteristics of inorganic and biologic dispersions. The repetition of observations after their initiation gives data on the velocity and mechanism of reactions, and permits one to follow the transformations which take place in living processes.

The various measurements afforded by the instrument, when suitably related, constitute a new system of analysis which it is proposed to call scopometry.

271 Central Park West.

ABSTRACT OF DISCUSSION

DR. J. A. KOLMER, Philadelphia: The work done by Dr. Exton in improving the measurements of turbidity will unquestionably be of particular value to chemists. He has already alluded to the work that he has done in estimating albumin, particularly in the urine, but there is also a distinct field of application and usefulness in immunology, because pathologists are appreciating, I think, with increasing frequency that precipitation plays an important part in the mechanism of some immunologic reactions. Up to within comparatively recent times, one has been obliged to evaluate or estimate immunologic precipitation by the naked eye, and since this is lacking in sensitiveness, I can foresee for Dr. Exton's work a definite value in the study of immunologic phenomena so far as it embraces precipitation, because an instrument such as the scopometer should and will greatly increase accuracy in the measurement of precipitates.

At present, I believe that the complement-fixation reaction is a more sensitive method of serum diagnosis than that of precipitation, but with an instrument such as the scopometer at one's disposal, one will probably be able to appreciate finer and more sensitive reactions. I really believe that the solving of some of the problems of immunologic reaction will be along the lines alluded to in this paper.

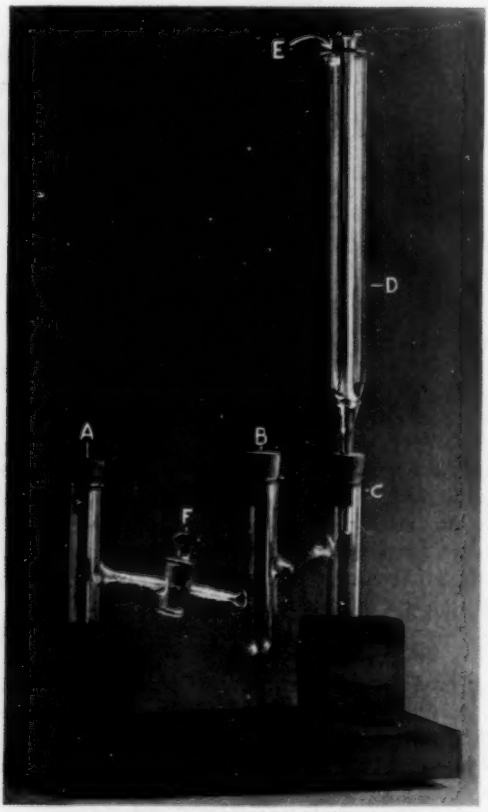
If I had my career in immunology to live over again I would go more deeply into the phenomena of physical chemistry as giving a real basis for the explanation of the various reactions of immunity.

DR. FRANK W. HARTMAN, Detroit: I can think of many applications for this apparatus. Pathologists are greatly indebted to Dr. Exton for his test of albumin in the urine. It has proved of great aid in accuracy and speed in this determination, and I feel that this is more or less a continuation along the same line, only it will apply to a much larger field in chemistry and immunology, as Dr. Kolmer has said, and perhaps, too, in the counting of red blood cells which is tedious, and the estimation of the number of bacilli in the vaccine; and there will be many other applications that will facilitate and make more accurate many laboratory determinations.

AN AID IN TESTING GASTRIC CONTENTS FOR LACTIC ACID*

E. M. Watson, M.D., M.Sc., London, Canada

"Any patient with a suspicion of gastric cancer whose test meal shows no hydrochloric acid but a definite amount of lactic acid has got cancer." This statement was published recently by Maclean.[1] It is also maintained by the same author that in many cases of carcinoma of the stomach, lactic acid is present in the gastric contents before appreciable symptoms of dyspepsia are manifest.



Apparatus used in testing gastric contents for lactic acid.

A declaration such as the one by Maclean should serve at least to stimulate renewed interest in the problem of lactic acid in the contents of the stomach from the standpoint of the early diagnosis of gastric carcinoma.

There are not, perhaps, any tests in the realm of clinical pathology which offer greater uncertainties concerning interpretation than those for lactic acid.

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* From the Laboratory of Pathological Chemistry, University of Western Ontario Medical School.

1. Maclean, Hugh: Modern Views on Digestion and Gastric Disease, London, Constable & Co., 1925, p. 108.

None of the available clinical tests can claim specificity, owing to the effect of interfering substances which may be present. The test most commonly used is probably Uffelmann's, but this is said to be neither sensitive nor reliable when applied directly to the contents of the stomach.[2] It is generally agreed that the best results are obtained by first extracting the lactic acid from the gastric fluid with ether, evaporating the ether, redissolving the residue in water and then applying the test to the aqueous solution.

I shall describe an apparatus whereby lactic acid may be extracted from small amounts of contents of the stomach such as are obtained during fractional gastric analysis.

METHOD

The device is shown in the accompanying illustration.

About 2 cc. of the material to be tested is placed in tube *A*, and a similar quantity of ether is added. A cork is placed in the mouth of the tube, and the communication between tubes *A* and *B* is closed by means of the stop-cock *F*. The apparatus is taken from the block, inverted several times and then replaced. After the ether has separated, the stop-cock is turned so that the connection between *A* and *B* is open. The contrivance is now tilted so that the ether but none of the gastric contents drains over from tube *A* into tube *B*. The stop-cock is again closed and the condenser (*D*), which until now has been removed from the apparatus, is placed in position, the stem passing through a cock in the mouth of tube *C*. The jacket of the condenser (*E*) is filled with finely chopped ice. The lower portion of *B* is immersed in a small beaker of hot water. When the ether has evaporated, the residue remaining in *B* is dissolved in distilled water, and the test for lactic acid is carried out on this solution. The whole procedure takes only a short time, and the ether recovered in tube *C* may be used again. The method is especially valuable in checking results obtained by the direct method of examination when these results are weak or doubtful.

The apparatus described in this paper was made by Mr. A. Barber, my technical assistant.

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2. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1927, p. 399.

General Review

FOCAL INFECTION AND "ELECTIVE LOCALIZATION"

A CRITICAL REVIEW *

W. L. HOLMAN, M.D.
TORONTO, ONT.

Focal infection has changed, with increased evidence, from a theory to a principle of infection. It has been often misunderstood and misinterpreted, and my object in this review is to attempt to bring together, if possible, reports of various investigations on disease processes made from different points of view, so that a general conception of the problem as a whole may be obtained. It necessarily involves the primary bases of infection and touches on practically every field of medicine. In a recent letter, I [1] have called attention to the prevalent confusion in the minds of many investigators in research and clinical medicine between the facts of focal infection and the hypothesis of elective localization as promulgated by Rosenow and his followers. This confusion is, I believe, unfortunate, since it diverts attention from the underlying principles of infection and decidedly overstresses the part played by bacteria, particularly during the early stages. In a review of this most complex problem, which takes in every organ and tissue in the body, I must needs limit myself. It is only within the last few years that the interest in, and the importance of, focal infection has been appreciated, although it has often been emphasized in the past history of medicine.

It is almost self-evident that practically all bacterial, protozoal and virus infections must have a portal of entry with a primary focus from which the distribution, if such occurs, follows. This is too broad a conception, however, and focal infection has come to have a special meaning. Billings [2] pointed out that a focus of infection may give rise to intoxication or focal infection (which means invasion from a focus), and, indeed, it is known that such a focus may be latent or permanently inactive. It is well to keep in mind this important difference between focus of infection and focal infection. Billings [3] defined a focus of infection as "a

* From the Department of Pathology and Bacteriology, University of Toronto.

1. Holman, W. L.: The Localization in Animals of Bacteria Isolated from Foci of Infection, J. A. M. A. **88**:424 (Feb. 5) 1927.

2. Billings, F., in discussion of Fontaine, B. W.: A Clinical Study of the End Results of Some Focal Infections, J. A. M. A. **74**:1629 (June 12) 1920.

3. Billings, F.: Focal Infection, New York, D. Appleton & Co., 1918.

circumscribed area of tissue infected with pathogenic micro-organisms." The term focal infection further implies that: 1. There exists, or has existed, a circumscribed lesion or focus. 2. The lesion is of bacterial nature and, as such, is capable of dissemination. 3. From the focus there has resulted systemic infection or infection of other contiguous or non-contiguous parts (Blum [4]).

Before considering the evidence which developed the present principle of focal infection, I shall mention some early references to this idea, which may be of interest. C. H. Mayo [5] cited Hippocrates as having recorded two cases in which eradications of infections of the mouth had relieved patients of rheumatic troubles of the joints. Abernethy [6] particularly stressed the relationship of the conditions in the digestive organs to a number of systemic diseases. In 1818, Rush [7] published observations made as early as 1801, which definitely indicated the curative effects of removing infected teeth in patients with nervous and general diseases, even when the external parts of the teeth were sound. Trousseau is quoted by Roethlisberger [8] as having first noted in 1865 the occurrence of angina preceding articular rheumatism. The first case of hyperthyroidism described by Graves [9] was in a woman convalescing from acute rheumatism. In 1869, Winge [10] reported a case of malignant endocarditis in a man who died of septicemia, originating from an abscess in the foot. Thus, it is seen that the conception of focal infection is not new.

It is necessary to consider in each patient what criteria are demanded or suggested before a focus of infection should be considered as the contributory factor to the focal infection and the conditions found in the patient. First, the foci must be found. It is not necessary that these foci show definite activity or trouble the patient, although this perhaps takes place most frequently; often, however, this does not occur. It is therefore only after painstaking effort that one can feel reasonably

4. Blum, S.: Focal Infections in Childhood, Am. J. M. Sc. **156**:681, 1918.

5. Mayo, C. H.: Focal Infection of Dental Origin, Dental Cosmos **64**:1206, 1922.

6. Abernethy, John: Surgical Observations on the Constitutional Origin and Treatment of Local Diseases, London, 1809.

7. Rush, Benjamin: Medical Inquiries and Observations **1**:199, 1818; reprinted in Duke, W. W.: Oral Sepsis in Its Relationship to Systemic Disease, St. Louis, C. V. Mosby Company, 1918.

8. Trousseau, A., quoted from Roethlisberger, P.: Neues ueber Untersuchung und Behandlung gewissen mit Polyarthritis kausal verknüpfter Tonsilliten, München. med. Wchnschr. **59**:408, 1912.

9. Graves, R. J.: London M. & S. J. **7**:516, 1835; quoted by Fischer, M. H.: Oedema and Nephritis, appendix, New York, John Wiley & Sons, 1921, p. 872.

10. Winge: Constatt's Jahresbericht **2**:95, 1870; quoted by Blum (footnote 4, p. 681).

sure of having found all the foci that are probably or possibly responsible for the condition. In this connection, statistical studies on healthy persons help in keeping an even course and prevent laying too much stress on what may be a mere coincidence or an expression of a general disease condition. It is also to be recognized that there are comparatively few completely healthy people and that investigators of particular conditions in special organs have a tendency to include in their controls all persons free from the illness being considered; it should be realized that these controls often have other diseases, possibly caused by focal infection, depending on innumerable preceding incidents and factors. Later, I will discuss and attempt to put in order the varying relationships of certain of these incidents and factors.

After the presence of foci of infection has been determined, it is next necessary to weigh the evidence for or against their importance in the given circumstances. Frequently, the local condition offers a clue, but not always. The evidence of a disease in an organ or tissue that has preceded the local condition is often helpful, but as this disease may have occurred a long time before, it is not uncommonly of questionable value. The finding of bacteria may sometimes be useful, and certainly the evidence of an infection of the blood stream is a great diagnostic help. However, because of the high invasive power of certain of these bacteria, such as the streptococcus group,[11] precaution should be observed against their presence being accepted as of overwhelming importance. The determination of the biologic type of streptococci is of some help, and when it suggests a particular portal of entry, such as the finding of *Streptococcus fecalis* or *Streptococcus salivarius* in the circulation, it may be of particular importance.[12] In connection with this phase of the subject, I believe that the work of Schönfeld,[13] Meyer and Schönfeld,[14] and Meyer[15] on the enterococcus is a useful advance in the better understanding of streptococci from the intestinal tract. I have emphasized the high resistant power of *Streptococcus fecalis* to heat and storage, but these authors have given further characteristics of enterococcus, such as its resistance to heat and to bile, and its ability to ferment esculin. The group certainly includes more than *Streptococcus fecalis*.

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11. Holman, W. L.: The Invasive Quality of the Streptococci in the Living Animal, Am. J. M. Sc. **153**:427, 1917.

12. Holman, W. L.: The Classification of Streptococci, J. M. Research **34**:377, 1916.

13. Schönfeld, H.: Zur Morphologie und Biologie der Stuhlstreptokokken, Centralbl. f. Bakteriol. **99**:388, 1926.

14. Meyer, K., and Schönfeld, H.: Ueber die Differenzierung des Enterococcus vom Streptococcus viridans und die Beziehungen beider zum Streptococcus lactis, Centralbl. f. Bakteriol. **99**:401, 1926.

15. Meyer, K.: Ueber hämolytische Enterokokken, Centralbl. f. Bakteriol. **99**:416, 1926.

The bacteriology of focal infection seems to be largely that of the streptococci, and the question of alterations in the long recognized types is today being actively discussed. Schottmüller,[16] who first clearly separated *Streptococcus viridans* from *Streptococcus hemolyticus,* and his followers (Wirth [17] and others) maintained the differentiation, while Morgenroth [18] and his school, Freund,[19] Kuczynski and Wolff,[20] and many others, believed that *Streptococcus viridans* was only a stage in the process of the reaction of *Streptococcus hemolyticus* to the defense mechanism of the body. It would take entirely too much space to analyze the experimental evidence on this problem, and this is scarcely the place for it. It may be pointed out, however, that dissociation,[21] temporary suppression of bacterial functions, mixed cultures, invasion of the experimental animal by its own micro-organisms, multiple infections in man and many other factors must be carefully considered. Few people today question that bacteria respond to the reactions of the animal body in infections and become altered in various ways, as has been so well shown by Bail.[22] But what the limitations of such alterations are, and the practical importance of certain of them, is by no means clear. The fundamental principles of bacteriology and the danger of animal experimentation must be kept in mind before the solution of this problem is complete. The early work by Rosenow [23] on transmutation has little to do with the problem of today. I discussed certain phases of his work several years ago.[24] It must not, however, be thought that focal infection

16. Schottmüller, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr. **50**:849 and 909, 1903.

17. Wirth, E.: Zur Kenntnis der Streptokokken, Centralbl. f. Bakteriol. **99**: 266, 1926.

18. Morgenroth, J., and Schnitzer, R.: Zustandsänderung der Streptokokken, Ztschr. f. Hyg. u. Infectionskrankh. **97**:77, 99 and 102, 1923; **99**:221, 1923. Schnitzer, R., and Munter, F.: Ibid. **99**:366, 1923. Schnitzer, R., and Amster, S.: Ibid. **101**:282, 1924; ibid. **102**:287, 1924.

19. Freund, R.: Ueber experimentelle Umwandlung des Streptococcus Viridans in den hämolytischen Zustand unter dem Einfluss des Rivanols, Deutsche med. Wchnschr. **49**:1146, 1923. Freund, R., and Berger, E.: Ueber Befunde von Streptokokken im Blut, ibid. **50**:625, 1924.

20. Kuczynski, M. H., and Wolff, E. K.: Untersuchungen über die experimentelle Streptokokkeninfektion der Maus: Ein Beitrag zum Problem der Viridanssepsis, Berl. klin. Wchnschr. **57**:777, 1920.

21. Hadley, P.: Microbic Dissociation, J. Infect. Dis. **40**:1, 1927.

22. Bail, O.: Die Infektiosität von Bakterien, Ztschr. f. d. ges. exper. Med. **50**:11, 1926.

23. Rosenow, E. C.: Transmutation Within the Streptococcus-Pneumococcus Group, J. Infect. Dis. **14**:1, 1914.

24. Holman, W. L.: The Relative Longevity of Different Streptococci and Possible Errors in the Isolation and Differentiation of Streptococci, J. Infect. Dis. **15**:293, 1914.

is in any way confined to the streptococcus group. Pneumococci, staphylococci, gonococci, and many other bacteria invade the body from a primary focus of infection, and the reason so much stress has been given to the streptococci is because they usually have a higher invasive power and are by far the most frequently encountered.

When blood cultures are negative, as so often occurs, other means have been suggested to determine the relative importance of the bacteria found in the suspected focus. One of these methods is that of Solis-Cohen,[25] who used what he called a pathogenselective method by growing the isolated bacteria from the respiratory tract in the patient's whole coagulable blood. A similar method with coagulable blood has been used by Kuczynski[26] to induce hemolytic streptococci to become anhemolytic and green producing. For years, Schottmüller had been using a similar test to determine relative virulence. Following the work of Ruge[27] and Phillip,[28] who believed that the patient's blood gave a better test of virulence than normal blood, a controversy arose. Wirth[17] clearly showed that the patient's blood did not help in estimating the relative virulence of streptococci.

Another method has been to test the sensitiveness of the patient to the isolated bacteria. It has long been suspected that anaphylaxis plays a part in this type of infection. Much work has been done, particularly with patients who have asthma, by means of skin tests with bacterial proteins, but generally the work has been unproductive. In attempting to develop a biologic classification, Davis[29] used sensitization experiments, and found that animals sensitized to the hemolytic streptococcus did not react with a strain of *Streptococcus viridans* from a patient with chronic infective endocarditis. Zinsser[30] believed that early in the course of infection the animal became sensitized and that subsequently, materials from the bacterial focus played a fundamental part in the injury of the animal. He and his associates further studied the problem of bacterial anaphylaxis with the pneumococcus[31] and streptococcus,[32] and found

25. Solis-Cohen, M.: Visceral Disease Due to Bacterial Infection of Apparently Normal Upper Respiratory Tract, J. A. M. A. **83**:824 (Sept. 13) 1924.

26. Kuczynski, M. H.: Untersuchungen über Ernährungen, Rassenbildung und Immunität bei Streptokokken, Klin. Wchnschr. **1**:1413, 1922.

27. Ruge, C.: Virulenzbestimmung der Streptokokken, Med. Klin. **7**:200, 1923.

28. Phillip, E.: Zur Virulenzfrage der Streptokokken, Klin. Wchnschr. **2**: 1025, 1923.

29. Davis, D. J.: Interrelations in the Streptococcus Group with Special Reference to Anaphylactic Reactions, J. Infect. Dis. **12**:386, 1913.

30. Zinsser, H.: Tuberculin Reactions and Specific Hypersensitiveness in Bacterial Infections, J. Exper. Med. **34**:495, 1921; Bacterial Allergy and Tissue Reactions, Proc. Soc. Exper. Biol. & Med. **22**:35, 1924.

31. Zinsser, H., and Mallory, T. B.: Bacterial Anaphylaxis with Pneumococcus, J. Immunol. **9**:75, 1924.

32. Zinsser, H., and Grinnel, F. B.: Allergic Reactions to the Hemolytic Streptococcus, J. Immunol. **10**:725, 1925.

that the latter might be living in foci long after the allergy had passed. They drew particular attention to the nonprotein substances in these experiments. Mackenzie and Hanger [33] tested a number of patients intracutaneously with the filtrates (and extracts) of hemolytic and nonhemolytic streptococci obtained from the interior of tonsils. Most adults (twenty-nine of thirty) gave positive reactions twelve hours after the injection, and in twelve infants under 6 months of age, the reactions were negative. They noted that a nonhemolytic strain from a patient with rheumatic fever gave an active filtrate after twenty-four but not after forty-eight hours' growth, while four strains from normal patients were practically inactive. The site of a previous injection was found to give a nonspecific accelerated reaction. Extracts were often more active, and some of these produced an immediate reaction. In a later study,[34] Mackenzie and Hanger found that some people react more to filtrates than to extracts. However, they could not find any relationship between these tests and any disease process. Sherwood and Stoland,[35] working with typhoid protein, found that guinea-pigs could be sensitized without giving the smooth muscle reaction of Dale, in fact, that the uterus was sometimes more than normally resistant. Derick and Andrewes [36] called attention to an interesting response in the skin of 50 per cent of normal rabbits to the sedimented cultures, living or killed, of nonhemolytic streptococci. Filtrates and other products gave negative results. The reaction occurred in from twenty-four to forty-eight hours, and on the eighth day a secondary reaction followed. The streptococci giving these phenomena were from nodules, the blood or the heart of patients with rheumatic fever (five of ten strains); the blood from a patient with subacute bacterial endocarditis (one of four); the urine of a nephritic patient (one), and a nodule from a rheumatic patient an anomalous strain. The results were negative with strains of viridans from normal throats, hemolytic streptococci, staphylococci and others. They concluded that the secondary reaction was not an example of the Arthus phenomenon. Kolmer [37] suggested that an injection of autogenous vaccine which caused an exacerbation in the secondary foci might give evidence of

33. Mackenzie, G. M., and Hanger, F. M.: A Study of Hypersensitiveness to Derivatives of Hemolytic and Non-Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **21**:442, 1924.

34. Mackenzie, G. M., and Hanger, F. M.: Allergic Reactions to Streptococcus Antigens, J. Immunol. **13**:41, 1927.

35. Sherwood, N. P., and Stoland, O. O.: Further Studies on Bacterial Anaphylaxis, J. Immunol. **10**:643, 1925.

36. Derick, C. L., and Andrewes, C. H.: The Skin Response of Rabbits to Non-Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **23**:116, 1925.

37. Kolmer, J. A.: Focal Infection from the Laboratory Standpoint, J. A. M. A. **87**:824 (Sept. 11) 1926.

importance. Herrold and Traut [38] studied the skin reactions with many bacterial filtrates and extracts and believed that more accurate titration of the skin-test-unit of filtrates of streptococci from chronic foci might be of value. They particularly studied the reactions in pneumonia. Birkhaug,[39] working with toxins from strains of nonmethemoglobin-forming streptococci from patients with rheumatic fever, found that a decidedly higher percentage of persons with a history of rheumatic fever gave positive skin reactions than did normal persons. It is to be noted, however, that the percentages are practically the same in the two groups in which he used filtrates of *Streptococcus scarlatinae* (1:2,000), *Streptococcus erysipelas* (1:1,000) and *Streptococcus viridans* (1:100 and 1:10), and only slightly higher with the rheumatic fever strain in a dilution of 1:1,000. It was only with more concentrated filtrates of the latter culture (1:100 and 1:10) that the difference was strikingly shown and may possibly be explained by the general hypersensitiveness of patients with rheumatic fever. The earlier work already quoted, would indicate that certain streptococci isolated from patients with rheumatic fever produce in culture a greater amount of substances causing skin reactions than the majority of streptococci from normal persons, but not necessarily from patients who have had rheumatic fever. It would have been well if the other filtrates that gave relatively high percentages of reactions in both groups in the dilutions used had been tested in comparable concentrations. It would appear from all these results that, by careful titration of dosage in intracutaneous tests, one may hope to find that the bacteria from the foci of infection produce substances to which the individual is particularly sensitive and that this may help as presumptive evidence that focal infection is active or has been active.

Other methods have also been tried in the attempt to discover whether the patient has reacted to the particular strains of bacteria isolated from the suspected focus. Among these is the agglutination test. In going through the literature, I have not found much evidence of this test being of practical importance, and I will therefore not burden this paper with a recital of the work done. Complement fixation, strongly advocated by Burbank and Hadjopoulos [40] and many others, may also be useful, but much careful statistical work must still be done to determine whether such evidence indicates a protective immunity or an increased suscepti-

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38. Herrold, R. D., and Traut, E. F.: Skin Reactions with Pneumococcal and Other Bacterial Filtrates and Extracts, J. Infect. Dis. **40**:619, 1927.

39. Birkhaug, K. E.: Rheumatic Fever, Bacteriologic Studies on a Non-Methemoglobin-Forming Streptococcus with Special Reference to Its Soluble Toxin Production, J. Infect. Dis. **40**:549, 1927.

40. Burbank, R., and Hadjopoulos, L. G.: Serologic Significance of Streptococci in Arthritis and Allied Conditions, J. A. M. A. **84**:637 (Feb. 28) 1925.

bility. De Niord [41] considered that a persistently high uric acid value for the blood was indicative of nuclear degeneration, which in turn may mean the presence of focal infection when other well known factors have been ruled out. He stated that elimination of all foci of infection was followed invariably by a return to normal of the uric acid value of the blood. I have not seen confirmation of these results. A number of investigators have attempted to show a relationship between lymphocytosis and focal infections. Among these are Daland [42] and Price,[43] who experimented with periapical infections of the teeth, but this work has not been of value in the hands of others. The most convincing evidence of such relationship, however, has been pragmatic. When the apparent focus of infection has been removed, there may be an exacerbation of the secondary focus at the time of operation (tonsillectomy, extraction of teeth et al.), or cure of the clinical condition may follow. This is the criterion on which the principle of focal infection is mainly founded and will be discussed later in this review.

An impressive number of experiments with the isolated bacteria in animals also has had a marked influence in establishing the principle of focal infection since the reproduction in the animal body of lesions similar to and often practically identical with those occurring naturally in man strongly suggests that these bacteria have the faculty to bring about such disease processes. However, the numerous factors in man and animals which determine the various localizations require careful analyses; these will be taken up under a later discussion and also under elective localization as developed by Rosenow and his school.

It may be advisable, therefore, first to review as briefly as possible the extensive literature which has collected about the different foci of infection and the disease processes looked on as the result of such infections. One cannot read far in the literature of focal infection without being impressed with the fact that the various workers stress the importance of the particular foci to which for one reason or another their attention has been drawn; it is therefore well to weigh as carefully as possible the relative importance of the various foci.

The foci about the teeth are held responsible for almost all known diseases, as are infected tonsils, the intestinal tract and many other infected sites. Sometimes the infection is supposed to start in the intestines and secondarily to infect the tonsils; sometimes the reverse

Include G-I tract as "focus"

41. De Niord, R. N.: Blood Chemistry as a Diagnostic Aid in Focal Infection, J. Dental Research **4**:435, 1922. De Niord, R. N., and Bixby, B. J.: Studies in Focal Infection, Preliminary Report, J. Lab. & Clin. Med. **7**:573, 1922.

42. Daland, J.: Lymphocytosis as Diagnostic Sign of Chronic Periapical Dental Infection in Adults, J. A. M. A. **77**:1308 (Oct. 22) 1921.

43. Price, W. A.: Some Systemic Expressions of Dental Infections, Ann. Clin. Med. **4**:943, 1926.

occurs, and the same process is suggested for all other foci. There is little doubt that such interrelationships occur, and it is my purpose to try to show what criteria are necessary to determine the sequence as well as some of the underlying reasons why certain foci may be more important than others in bringing about systemic infections in the body. It is immaterial whether I discuss tonsils or teeth first, since both have received the bulk of attention. I will therefore first review some of the work that has been done on the question of infected tonsils.

TONSILS

The anatomy of the tonsils and their environment should be carefully studied; their functions, if possible, should be determined, while the factors affecting them as part of the general economy must not be overlooked. These collections of lymphoid tissue with their epithelium-lined crypts are normally protected from the bacteria of the mouth by the pillars of the tonsils and the mechanism described by Bloomfield.[44] The function of the tonsil has not been definitely determined. Maclachlan [45] discussed it in his study of tonsillitis, and there have been many theories on the subject. Blum [46] looked on the tonsils as excretory organs for the cervical glands and gave a number of other reasons for their existence. Digby [47] considered that they play an important function in immunizing the body against pathogenic bacteria. This author also called attention to the presence in man and the dog of the protuberant type of tonsil, and in the cat, rabbit and cow of the tubular type. From clinical observation, Canfield [48] saw a relationship between tonsils and adenoids and the functioning of the thyroid gland. He believed the former to be most essential to the child's welfare in the four or five years of his life when he is "potentially a hyperthyroid case." If the child is deprived at this time of his adenoids and tonsils, their importance to his welfare becomes evident by his increased susceptibility to infections. It is also considered that they may have a function in regulating growth, and the possibility of internal secretions has, of course, been advanced. Schmidt [49]

44. Bloomfield, A. L.: The Dissemination of Bacteria in the Upper Air Passages: I. The Circulation of Foreign Particles in the Mouth, Am. Rev. Tuberc. **5**:903, 1922.

45. Maclachlan, W. W. G.: Tonsillitis: A Histo-Pathological Study, Publications of University of Pittsburgh Medical School, 1912.

46. Blum, S.: Tonsils Excretory Organs for Cervical Glands: Preliminary Report, Arch. Pediat. **32**:837, 1915; The Proper Position of Tonsillectomy in Pediatrics, ibid. **32**:816, 1915.

47. Digby, K. L.: Immunity in Health: The Function of the Tonsils and other Subepithelial Lymphatic Glands in the Bodily Economy, New York, Oxford University Press, 1919.

48. Canfield, R. B.: Focal Infections in Medical Diseases, Ann. Clin. Med. **4**:1058, 1926.

49. Schmidt, V.: The Function of the Tonsils, Ugesk. f. Laeger **88**:613, 1926; abstr. Am. J. M. Sc. **173**:146, 1927.

found that after massaging the tonsils of healthy persons, a leukopenia occurred which was caused, he believed, by an antibody forced into the blood stream. The same procedure on inflamed tonsils produced a polymorphonuclear leukocytosis.

Whatever the function of the tonsils and adenoids may be, it is generally recognized that they often become sites for bacterial implantation. The bacteriology of the tonsils has received a great deal of attention, and it is unnecessary in this place to review all the literature. Davis [50] carried out a number of studies but as most of these dealt with patients having secondary infections, his work and that of a number of others will be considered under the headings of the different secondary sites of infection. Henke and Reiter [51] also reported cases in which a definite infection, such as tonsillitis, was present but stated further that both hemolytic and nonhemolytic streptococci are normally present in the tonsil. Kellert [52] found that enlarged and infected tonsils were of common occurrence in the healthy adult and that inflammatory changes suggestive of infection were present in nearly all tonsils. Keilty [53] emphasized the difference already mentioned between a focus of infection, which, remaining inactive, may be merely a potential site of infection, and one unloading its infection into the circulation. The importance of this in interpreting the bacteriologic manifestations is self-evident. Caylor and Dick [54] considered that, beyond the first years of life, there were no tonsils in which pathologic changes could not be found, and, therefore, that quantitative bacteriology was of more aid than qualitative bacteriology in determining the condition of a tonsil after removal. Nakamura [55] found streptococci to be the commonest bacteria in extirpated tonsils and that hemolytic streptococci increased in incidence and number with the approach of cold weather and the prevalence of tonsillitis and similar infections. From a study of 147 pairs of tonsils, Julianelle [56] reported hemolytic streptococci in 133, or 90.4 per cent.

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50. Davis, D. J.: Bacteriology and Pathology of the Tonsils with Especial Reference to Chronic Renal and Cardiac Lesions, J. Infect. Dis. **10**:148, 1912.

51. Henke, F., and Reiter, H.: Zur Bedeutung der hämolytischen und anhämolytischen Streptokokken für die Pathologie der Tonsillen, Berl. klin. Wchnschr. **49**:1927, 1912.

52. Kellert, E.: The Pathological Histology of Tonsils Containing Hemolytic Streptococci, J. M. Research **41**:387, 1920.

53. Keilty, R. A.: The Tonsils as Foci of Infection, J. M. Research **42**: 315, 1921.

54. Caylor, H. D., and Dick, G. F.: Quantitative Bacteriology of the Tonsils, J. A. M. A. **78**:570 (Feb. 25) 1922.

55. Nakamura, T.: The Bacteriology of Extirpated Tonsils and Its Relation to Epidemic Tonsillitis, Ann. Surg. **74**:24, 1924.

56. Julianelle, L. A.: A Bacteriologic Study of Extirpated Tonsils, J. Lab. & Clin. Med. **9**:69, 1924.

There is considerable evidence to show that tonsillectomy definitely reduces the incidence of hemolytic streptococci in throats. This has been demonstrated by many.[57] Doull [58] did not find any significant difference in the liability of tonsillectomized and nontonsillectomized children to develop scarlet fever. Gottlieb [59] was convinced that *Streptococcus viridans* was present in all tonsils and was usually of low virulence, while *Streptococcus hemolyticus,* often present, was definitely virulent, if a corollary may be drawn from the effect of streptococci on the rabbit as compared to man. This observation has been general and is of particular interest in the problem of elective localization; it will be more fully considered under this head. Tonsillectomy is an old surgical procedure. Glover [60] gave a good historical account of it, and it is evident that tonsils were removed because of changes brought about by inflammation as early as A.D. 10. However, most tonsils were probably removed in the early days because of enlargement. The operation has become so commonplace today that a number of investigators have rightly protested and have demanded that a more careful study be made in each case to obviate unnecessary tonsillectomies. Comroe,[61] Blum,[4] Alvarez [62] and others have helped to formulate the necessary conditions that call for the operation. Fein [63] did not believe that an acute infection, capable of inducing septicemia, could remain in the tonsil without causing visible signs of inflammation or subjective symp-

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57. Nichols, H. J., and Bryan, J. H.: Tonsils as Foci of Infections in Streptococcus Hemolyticus Carriers, J. A. M. A. **71**:1813 (Nov. 13) 1918. Simmons, J. S., and Taylor, R. E.: Bacterial Carriers in the Upper Respiratory Tract, ibid. **72**:1885 (June 28) 1919. Pilot, I., and Davis, D. J.: J. Infect. Dis. **24**:386, 1919. Tongs, M. S.: Hemolytic Streptococcic in the Nose and Throat with Special Reference to Their Occurrence After Tonsillectomy, J. A. M. A. **73**:1050 (Oct. 4) 1919. Van Dyke, H. B.: Hemolytic Streptococci in the Normal Throat After Tonsillectomy, ibid. **74**:448 (Feb. 14) 1920. Meyer, J.; Pilot, I., and Pearlman, S. J.: Bacteriologic Studies of the Upper Respiratory Passages: IV. The Incidence of Pneumococci, Hemolytic Streptococci and Influenza Bacilli (Pfeiffer) in the Nasopharynx of Tonsillectomized and Non-Tonsillectomized Children, J. Infect. Dis. **29**:59, 1921.

58. Doull, J. A.: A Note on the Relationship of Tonsillectomy to the Occurrence of Scarlet Fever and Diphtheria, Pub. Health Rep. **39**:1833, 1924.

59. Gottlieb, M. J.: The Virulence of Streptococci Isolated from Material Expressed from the Tonsils, New York State J. Med. **20**:378, 1921.

60. Glover, E. E. V.: Historical Account of Tonsillectomy, Brit. M. J. **2**: 685, 1918.

61. Comroe, J. H.: The Use and Abuse of the Tonsil, J. A. M. A. **63**:1367 (Oct. 17) 1914.

62. Alvarez, W. C.: Lessons to Be Learned from the Results of Tonsillectomies in Adult Life: Observations in More Than Three Hundred Cases, J. A. M. A. **80**:1513 (May 26) 1923.

63. Fein, J.: Die Tonsillen als Einbruchspforte für Infektionen und die Indikationen für die radikalen Tonsillenoperationen, Med. Klin. **19**:306, 1923.

toms. He considered that recovery from distant symptoms was more common without tonsillectomy than after it. Kaiser [64] followed the results of tonsillectomy on a large number of children, and his conclusions are of particular value.

The conditions that lead to the early invasion and early local infections in the tonsils are probably the same as those giving rise to the so-called "common cold" and will be taken up later in this review. I have already indicated and it has been shown in the studies quoted that during the course of inflammatory reactions in the tonsils, closure of the crypts is liable to occur. In this contingency, the infected material cannot be readily forced to the surface by pressure. It has further been shown that small ulcers are frequently formed in the depths of these crypts. Crowe [65] demonstrated that the epithelium lining the crypts of the tonsil differs from that covering the surface, the former having papillae and a rich network of capillaries. The destruction of this epithelium was the most common pathologic change in chronic tonsillitis. In his opinion, this capillary bed opens the way to direct infection of the blood stream. Citron [66] demonstrated the importance of a resulting exacerbation of symptoms after compression of the tonsils. Kuczynski [67] showed that pressure on the tonsil could force bacteria into the circulation, and Schmidt [49] found that such a procedure altered the cellular composition of the blood. These results and the knowledge of the constant periodic compression of the tonsils in swallowing would strongly suggest that this mechanism of infection must be common and that the rôle of the tonsils in focal infection is therefore more important than that of many other infected foci. Fraenkel [68] noted in autopsies on fifteen patients who died from pyemia following tonsillitis that a primary direct infection of the tonsillar veins had occurred and that this had further involved the jugular vein. Infection of the kidney following acute or chronic tonsillitis has been frequently reported, and a close relationship between

64. Kaiser, A. D.: Effect of Tonsillectomy on General Health in Five Thousand Children, J. A. M. A. **78**:1869 (June 17) 1922; Effect of Tonsillectomy on the General Health of Twelve Hundred Children as Compared with an Equal Number Not Operated on, ibid. **83**:33 (July 5) 1924; Tonsillectomy in Children, Indications Based on End-Results, ibid. **87**:1012 (Sept. 25) 1926.

65. Crowe, S. J.: Direct Blood Stream Infection Through Tonsils, Arch. Int. Med. **33**:473 (April) 1924. Tanaka, M., and Crowe, S. J.: Direct Blood Stream Infection Through Tonsils, Arch. Otolaryng. **1**:510 (May) 1925.

66. Citron, J.: Die Tonsillen als Eingangspforte für Infektionen, Deutsche med. Wchnschr. **46**:340, 1920.

67. Kuczynski, M. H.: Nephritisstudien, Virchows Arch. f. path. Anat. **227**: 186, 1920.

68. Fraenkel, E.: Ueber postanginöse Pyaemie, Deutsche med. Wchnschr. **52**:93, 1926.

tonsillar infections and rheumatism, chorea, arthritis, heart disease, various nervous diseases and many other conditions has been repeatedly emphasized. These will be considered later under the various headings of the secondary foci.

TEETH

It has already been shown that infected teeth have long been suspected as causative factors in local and systemic disease processes. James I of Scotland is reported to have had badly decayed teeth and to have suffered from severe chronic rheumatism. On an ancient physician's signboard (1623) in the Royal College of Surgeons, London, is shown an alveolar abscess about to be lanced.[69] There is therefore evidence throughout history that teeth have brought trouble, as well as comfort, to mankind.

The histologic anatomy of the teeth and jaws usually receives only scant attention in the medical course. It is evident, however, that it must be studied in great detail in order to appreciate what are the conditions leading to foci of infection and what favors possible focal infection from these parts. Schottmüller [70] did not believe that alveolar abscesses or infectious foci in the pulp of teeth had the properties of septic foci, but few investigators have agreed with him.

Box [71] has given a short and useful description of the minute anatomy of the gingivae, pointing out that the thinness of the epithelium covering the gingival crevice, the occasional break in the surface and the imperfect junctions render it the weakest link in the chain of epithelial covering in the mouth. He also described the extremely rich blood supply. Beckwith, Simonton and Williams [72] studied the histology of the gum in pyorrhea and could not find a reason to ascribe the cause of pyorrhea to any single micro-organism. Duke,[73] in agreement with practically all investigators, has emphasized that there are many chief causes and several important contributing causes of pyorrhea. An alveolar abscess, or as Colyer [74] preferred, "chronic osteomyelitis," has two sources of

69. Mark, L.: Art and Medicine, London, 1906.

70. Schottmüller, H.: Ueber den angeblichen Zusammenhang zwischen Infektionen der Zähne und Allgemeinerkrankungen, Deutsche med. Wchnschr. **48**:181, 1922.

71. Box, H. B.: The Evolution of the Periodontal Pus Pocket, Canad. Dental Res. Foundation, 1921, Bull. 1; Studies in Periodontal Pathology Including Study Upon the Mechanics of Occlusion by G. R. Anderson and a Summary of the Signs of Incipient Periodontal Disease by H. B. Box, ibid., 1924.

72. Beckwith, T. D.; Simonton, F. V., and Williams, A.: A Histologic Study of the Gum in Pyorrhea, J. Am. Dental A. **12**:129, 1925.

73. Duke, W. W.: Oral Sepsis in Its Relationship to Systemic Disease, St. Louis, C. V. Mosby Company, 1918.

74. Colyer, S.: Chronic Infection of the Jaws, New York, The Macmillan Company, 1926.

origin; the first and least common is that following the progress of pyorrhea, the second more common source is from the root canal of infected teeth. The problem of dental caries thus becomes important. Mummery [75] gave an excellent account of the structure of teeth in relation to dental disease as has also Box,[76] who particularly pointed out the factors which cause disturbances of the circulation of blood in the pulp.

The bacteriologic literature on these two conditions is extensive, but it is beyond the scope of this article to analyze the bacteriologic cause, if such exists, of either pyorrhea or dental caries per se. The important point in these conditions is that portals of entry for pathogenic bacteria exist and that among them the greatest danger is once more believed to be the streptococci, as Hartzell and Henrici,[77] Henrici and Hartzell,[78] Kordenat,[79] Thompson,[80] Fisher [81] and a long list of others emphasized. The great mass of work to be reviewed under the different headings is also based on the importance of the streptococci. Hall [82] called attention to microbic changes in the saliva which depended on the pabulum present.

Both types of these infections about the teeth are extremely common, and the problem of how best to discover such foci is therefore important. Pyorrhea and caries are usually readily diagnosed. Acute alveolar abscesses also do not offer difficulties, but in chronic osteomyelitis and periapical abscesses about nonvital and even vital teeth, the diagnosis is often difficult. Here a roentgenogram is useful in interpreting the results. Berwick [83] showed that in 10 per cent of cases teeth showing roentgenographic changes did not show growth in culture, and he concluded

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75. Mummery, J. H.: The Structure of Teeth in Relation to Dental Disease, Med. Res. Council, Special Report Series, no. 70, London, 1922.

76. Box, H. B.: The Dentinal-Cemental Junction, Histological and Histo-Pathological Studies of the Dental Pulp, Canad. Dental Res. Foundation, 1922, Bull. 3 and 4.

77. Hartzell, T. B., and Henrici, A. T.: A Study of Streptococci from Pyorrhea Alveolaris and from Apical Abscesses, J. A. M. A. **64**:1055 (March 27) 1915; The Pathologenicity of Mouth Streptococci and Their Rôle in the Etiology of Dental Diseases, J. Nat. Dental A. **4**:477, 1917.

78. Henrici, A. T., and Hartzell, T. B.: The Bacteriology of Vital Pulps, J. Dental Research **1**:419, 1919.

79. Kordenat, R. A.: The Occurrence of Hemolytic Streptococci About the Teeth, J. Dental Research **3**:63, 1921.

80. Thompson, M. J.: An Experimental Study of the Streptococci Found in Pyorrhoea Alveolaris, Edinburgh M. J. **32**:781, 1925.

81. Fisher, J. H.: Pyorrhea Alveolaris: The Rôle of Certain Micro-Organisms Found in the Lesions, Am. J. Path. **3**:169, 1927.

82. Hall, I. C.: Bacterial Factors in Pyorrhea Alveolaris: I. Microbic Changes in Saliva, J. A. M. A. **81**:1676 (Nov. 17) 1923.

83. Berwick, C. C.: The Bacteriology of Peridental Tissues Radiographically Suggesting Infection, J. Infect. Dis. **29**:537, 1921.

that the proof of any definite relationship between dental infection and systemic disorder is possible in only a small percentage of suspected cases. Pulpless teeth are those which most frequently show periapical infection. Haden [84] found that 91 per cent of 500 patients had pulpless teeth and that 68 per cent had periapical rarefaction; in a later study [85] of 1,500 teeth he found that of those giving a positive culture and also positive roentgenographic evidence suggesting infection, 4.8 per cent were vital and 62.8 per cent were pulpless, while 46.2 per cent of the pulpless teeth with negative roentgenographic evidence gave positive cultures. Antonius and Czepa [86] reported that 66 per cent of 225 patients with various diseases showed roentgenographic evidence of an infectious process about the teeth and that this was twice as many as had chronic tonsillitis. Price [87] believed that extensive zones of rarefaction in dental infection in nonsusceptible persons indicated a high resistance.

Rodway [88] divided oral sepsis into three classes: (1) Sepsis from neglect—tartar, debris and gingivitis without pyorrhea; (2) periapical infection about teeth which had become nonvital, artifically or from caries; (3) chronic general periodontitis. He emphasized the extent of the periodontal membrane as an absorbing surface when ulcerated by estimating that this membrane about one tooth would form a triangle with sides measuring about three fourths of an inch. Brockbank [89] divided his cases into two groups: (1) apyrexial, in which myositis, fibrositis, neuritis, arthritis, phlebitis and a type of rheumatism following fatigue were the common occurrences; (2) pyrexial, in which acute tonsillitis, arthritis, septic endocarditis and myastheniacordis were the results. It is interesting that he and many others have noted this secondary involvement of the tonsil following dental infection and that the reverse has also been reported. Irons,[90] for example, considered that occasionally the lesions that developed about the roots of pulpless teeth were as truly metastatic as were those of iritis and arthritis.

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84. Haden, R. L.: The Incidence of Pulpless Teeth, J. Am. Dental A. **11**: 730, 1924.

85. Haden, R. L.: A Bacteriological Study of Chronic Periapical Dental Infection, J. Infect. Dis. **38**:486, 1926.

86. Antonius, E., and Czepa, A.: Dental Pathology and Internal Disease, Wien. Arch. f. inn. Med. **2**:293, 1921; abstr., J. A. M. A. **76**:1327 (May 7) 1921.

87. Price, W. A.: Dental Infections and Related Degenerative Diseases, J. A. M. A. **84**:254 (Jan. 24) 1925.

88. Rodway, B. J.: Dental Conditions Likely to Form Sources of Infection, Brit. M. J. **1**:564, 1926.

89. Brockbank, E. M.: Dental Sepsis and Septicemia, Brit. M. J. **1**:562, 1926.

90. Irons, E. E.: Chronic Systemic Infections and Their Sources, J. A. M. A. **76**:627 (March 5) 1921.

Gilmer [91] warned against the too prevalent belief that pulpless teeth must all be extracted. He emphasized that careful dentistry can save many such teeth. He further pointed out that the stress put on roots by the attachment of bridgework may often invite infection. Colyer [74] showed that the procedure for correcting teeth in children not infrequently caused permanent damage to the jaw. Box [92] and Anderson [93] have also emphasized the importance of malocclusion as the fundamental mechanical cause of local lowered resistance leading to infection. Alvarez [94] protested against the reckless extraction of teeth and favored a conservative attitude. It should be repeatedly urged that careful study of the problem of focal infection as a whole be made in every case, since multiple infections and the interrelationships of organs and tissues are basic considerations. In the teeth, as in the tonsils, the numerous reports show that the results following removal or cure of dental foci have been the determining proof that the responsible foci have been found. Failures are too frequently forgotten and the various contributing, and often essential, secondary factors are neglected.

I shall not now review the many diseases for which dental infection has been held responsible, as these will be considered later. It may be pointed out, however, that infection about the teeth, with the rich capillary circulation, particularly in the region of ulcerations, the frequent movement of the teeth in mastication, especially with malocclusion, which interferes with the curative processes, the ready access of bacteria and many other factors make such infected foci potentially more dangerous than those in other relatively immobile and better protected parts.

GASTRO-INTESTINAL TRACT

The gastro-intestinal tract constitutes a large area for possible infection and, taken in general, it has received considerable attention as a focus for focal infection. It will be unnecessary to review the anatomy in this article, and only occasional reference will be made to certain features of it. This tract has further been extensively studied as the seat of secondary infection, more particularly in the occurrence of ulcers in the stomach, duodenum and colon. I shall consider it first as a primary focus.

The recognition of the relationship between gastro-intestinal disturbance and secondary diseases and general health is as old as history.

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91. Gilmer, T. L.: Periapical Infection, Dental Cosmos, October, 1924; Miscellany, J. A. M. A. **84**:59 (Jan. 3) 1925.

92. Box (footnote 71, second reference).

93. Box, H. K.: Studies in Periodontal Pathology: Including Study Upon the Mechanics of Occlusion by Anderson, G. R., and a Summary of the Signs of Incipient Periodontal Disease, Canad. Dental Res. Foundation, 1924.

94. Alvarez, W. C.: A Protest Against the Reckless Extraction of Teeth, J. A. M. A. **73**:1179 (Oct. 18) 1919.

In his treatise on personal hygiene, Cornaro [95] emphasized the importance of diet and other secondary factors for the attaining of a healthy old age. Abernethy [6] also stressed its importance as the cause of local diseases affecting other parts of the body. A host of similar references is available. The consideration of diet and the intestinal flora and the problems surrounding intestinal absorption of bacteria and constipation must be only lightly touched on, although not infrequently these are the determining factors in infection from the intestines.

The majority of bacteria do not readily invade the body through the healthy intestinal mucosa, although the work of Adami [96] on subinfection gave evidence that such could occur. However, an intestinal mucosa which remains in perfect health throughout life must be extremely rare, and conditions favoring invasion are unquestionably frequently present. Moody and Irons [97] were unable to obtain evidence of invasion, using *B. pyocyaneus, B. prodigiosus* and *Streptococcus hemolyticus* introduced by stomach tube in dogs; Holman and Fernish [98] showed that *B. anthracis* given in gelatin capsules did not infect guinea-pigs, although the bacteria could be recovered from the feces for many days. Warren and Whipple [99] further showed that even after extensive injury to the intestinal mucosa, there was no increase in invasion of the bacteria normally present. All this and much other evidence clearly indicate that the conditions favoring invasion, which undoubtedly often does take place, are imperfectly understood. It may well be the case that such extreme destruction of mucosa in an otherwise healthy animal results in mobilization of the defensive mechanism which would be absent if the injury were a great deal less but more prolonged and causing only a slight stimulus to the general reaction of the body. Such conditions as I suggest are present in many cases of intestinal irritation with diarrhea or in the fatigued state of constipation. Local and general conditions play their part, and of these I believe that the state of the capillaries in the intestinal wall, as influenced by the nervous system in so many ways, is the important factor. Alvarez [100] discussed the origin of the so-called symptoms of autointoxication in constipation, and the resulting upset of

95. Cornaro, L.: Sure Methods of Attaining a Long and Healthy Life, trans. by W. Jones, Edinburgh, M'Caslan, 1771.

96. Adami, J. G.: Subinfection, J. A. M. A. **33**:1509 (Dec. 16) 1899; ibid. **33**:1572 (Dec. 23) 1899.

97. Moody, W. B., and Irons, E. E.: Invasion of Body by Bacteria from Intestinal Tract, J. Infect. Dis. **32**:226, 1923.

98. Holman, W. L., and Fernish, C. A.: Studies on B. Anthracis from the Feces of Guinea-Pigs Fed with Anthrax Material, Am. J. Hyg. **3**:640, 1923.

99. Warren, S. L., and Whipple, G. H.: Roentgen-Ray Intoxication, J. A. M. A. **81**:1673 (Nov. 17) 1923.

100. Alvarez, W. C.: Origin of the So-Called Auto-Intoxication Symptoms, J. A. M. A. **72**:8 (Jan. 4) 1919.

the capillary system is evidenced by the course of events. First, there is the stage of stimulation with flushed skin and general well being. Then follows the fatigue stage with pallor, headache and general depression, all evidence of poor capillary circulation. The removal of the cause results in rapid reflex improvement of cellular nutrition in all parts. I believe that these conditions favor bacterial invasion, and, as will be discussed later, help to determine the localization of the invading bacteria in the various tissues, not only those entering the circulation from the intestines but also those coming from other foci. I consider that this is one of the important ways that intestinal conditions affect focal infections.

Bacteria vary greatly in their invasive power, and among the most invasive are the streptococci. This may be due to their parasitic life and the development of a metabolism approaching that of the local tissue; as a consequence, they bring about comparatively little reaction at the portal of entry and only cause marked reactions in more distant tissues. The streptococcic flora of the intestine is far from constant and certainly depends on many factors. Miller and Smith [101] suggested the favoring effect of achlorhydria in increasing the number of streptococci in the intestine. Meyer [102] regarded the enterococcus as of great pathologic importance in most of the secondary infections in the abdominal cavity. The high incidence of *Streptococcus fecalis* determined by fermentation tests with lactose, mannit and salicin, as reported by Price [103] in infected teeth, and the occasional finding of this type by Thompson [80] and others in pyorrhea, would definitely suggest an intestinal origin for these infections, although the majority of investigators found *Streptococcus salivarius* and other forms suggesting their derivation from the oral cavity.

Another type of infection from the intestines occurs when definite lesions are present, such as those in typhoid fever, amebic and bacterial dysentery, ulcerative colitis and ulcers of the stomach and duodenum. The number of reports in the literature showing infection of the blood stream with streptococci in these conditions is impressive. The association or after-occurrence of the types of infection that are being considered further inclines one to look on these types as having gained entrance at the site of the lesions of the ulcers, where a rich capillary bed and other factors favor an invasion. The arthritis and other conditions following dysentery may be considered as probably being of such

101. Miller, S., and Smith, F. B.: An Investigation of Gastric Function in Chronic Arthritis and Fibrositis, Quart. J. Med. **20**:271, 1927.

102. Meyer, K.: Die Bedeutung des Enterokokkus für die Infektionen der Harn und Gallenwege, Klin. Wchnschr. **32**:2291, 1924.

103. Price, W. A.: Dental Infections and the Degenerative Diseases, Cleveland, 1923, vol. 1 and 2.

origin. The observations of Barrow and Armstrong [104] in chronic arthritis and of Mills [105] in infections of the eye with associated intestinal protozoa may also possibly be thus explained.

Gastroduodenal Ulcers.—The gastro-intestinal tract may also be the seat of secondary infections from primary foci such as tonsils and teeth. The experimental work of Rosenow [106] on ulcers of the stomach and duodenum was of great importance in the development of this phase of the subject, but as it deals primarily with the problem of "elective localization," it will again be considered under that heading. Haden [107] had results similar to those of Rosenow, and his work will also be reviewed later, as will the reports of Nakamura [108] and Hufford.[109] McMeans [110] did not believe that the lesions usually produced by experimental bacteremia represented the initial stage of gastric ulcer as it is found in man, and he did not find evidence for "elective localization" in his extensive study with many types of bacteria. Of particular interest in this place is the recovery by Rosenow [111] of streptococci from ulcers produced by Mann and Williamson in dogs, which certainly suggested the secondary nature of such an invasion and how important the region of lowered resistance is in infection. A second point apparently not fully appreciated by Rosenow was that the infection came from the animal itself, and emphasizes an inherent error always present in experimental bacteriology when animals are used.

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104. Barrow, J. V., and Armstrong, E. L.: Intestinal Protozoa and Chronic Diseases with Reference to Chronic Arthritis, Illinois M. J. **67**:427, 1925.

105. Mills, L.: Ocular Disease Occurring in the Course of Nondysenteric Amebiasis, J. A. M. A. **87**:1176 (Oct. 9) 1926.

106. Rosenow, E. C.: Ulcer of the Stomach by Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913. Rosenow, E. C., and Sanford, A. H.: Bacteriology of Ulcer of the Stomach and Duodenum in Man, J. Infect. Dis. **17**:219, 1915. Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, ibid. **19**:333, 1916; Focal Infection and Elective Localization of Bacteria in Appendicitis, Ulcer of the Stomach, Cholecystitis, and Pancreatitis, Surg. Gynec. Obst. **23**:19, 1921; Etiology of Spontaneous Ulcer of Stomach in Domestic Animals, J. Infect. Dis. **32**:384, 1923.

107. Haden, R. L., and Bohan, P. T.: Focal Infection in Peptic Ulcer, J. A. M. A. **84**:409 (Feb. 7) 1925; The Elective Localization of Bacteria in Peptic Ulcer, Arch. Int. Med. **35**:457 (April) 1925.

108. Nakamura, T.: Focal Infection, Gastric Ulcer and Arthritis, Ann. Surg. **74**:29, 1924.

109. Hufford, A. R.: Elective Localization of Streptococci from Peptic Ulcer in Man, Proc. Staff Meeting, Mayo Clinic **5**:11, 1927.

110. McMeans, J. W.: Concerning the Gastric Lesions Observed in Experimental Bacteremia, Arch. Int. Med. **22**:114 (July) 1918.

111. Rosenow, E. C.: The Specificity of the Streptococcus of Gastroduodenal Ulcer and Certain Factors Determining Its Localization, J. Infect. Dis. **33**:248, 1923.

It can scarcely be denied that infection plays an important rôle in the life cycle of gastro-intestinal ulcers, but that it takes the dominant part in the initial phase has certainly not been proved. The theories on the etiology of these ulcers are numerous and have been frequently reviewed. Karsner [112] gave a short review up to 1925. Ulcers frequently occur in many animals without experimental intervention, as many investigators have shown. Rosenau and Anderson [113] noted lesions and ulcers in the stomachs of 1,897 guinea-pigs, or 66 per cent of 2,882 guinea-pigs dying as the result of injections of diphtheria toxin. In those dying between two and three days after the injection, 77 per cent showed the lesion. Nikolaeff [114] showed that all concentrations of diphtheria toxin check the secretion of the suprarenals and that this may have a bearing on the susceptibility of guinea-pigs to this toxin. Carlson [115] reported that about 75 per cent of dogs with experimental parathyroid tetany showed ulcers, but that cats so treated did not show this condition; he believed that the dog, of all experimental animals, is the one most prone to develop ulcers in the duodenum and pylorus without experimental interference. Friedman and Hamburger [115] produced acute ulcers by silver nitrate and partial pyloric obstruction. By repeated injection of epinephrine in the dog Friedman [116] obtained ulcers in the duodenum; and later,[117] after removal of the suprarenals in dogs and rabbits and thyroidectomy of one side and various combined operations, he concluded that hypofunction of the suprarenals caused lesions in the duodenum, while the hypofunction of both thyroid and suprarenals did not produce lesions in either. In a further study,[118] he demonstrated that the injection of epinephrine alone produced duodenal lesions and that

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112. Karsner, H. T.: The Pathology of Peptic Ulcer of the Stomach, J. A. M. A. **85**:1376 (Oct. 31) 1925.

113. Rosenau, M. J., and Anderson, J. F.: A Stomach Lesion in Guinea-Pigs Caused by Diphtheria Toxine, Hyg. Lab. Bull. no. 32, Washington, 1906.

114. Nikolaeff, M. P.: Ueber den Einfluss einiger pathogener Bakterien und ihrer Toxine auf die Funktion der isolierten Nebenniere, Ztschr. f. d. ges. exper. Med. **49**:27, 1926.

115. Carlson, A. J., in discussion on Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Ulcer, J. A. M. A. **63**:380 (Aug. 1) 1914.

116. Friedman, G. A.: The Experimental Production of Lesions, Erosions, and Acute Ulcers in the Duodenal Mucosa of Dogs by Repeated Injection of Epinephrin, J. M. Research **32**:95, 1915.

117. Friedman, G. A.: The Influence of Removal of the Adrenals and One-Sided Thyroidectomy Upon the Gastric and Duodenal Mucosa: The Experimental Production of Lesions, Erosions and Acute Ulcers, J. M. Research **32**: 287, 1915.

118. Friedman, G. A.: The Experimental Production of Lesions, Erosions and Acute Ulcers in Rabbits by Repeated Injections of Pilocarpin and Adrenalin, J. M. Research **38**:449, 1918.

the injection of pilocarpine alone acted on the gastric mucosa. Smith [119] introduced bile with an excess of 0.5 per cent hydrochloric acid into the stomach of cats and dogs and found superficial ulcers in the mucosa; he found that neither of these substances had any effect alone. Mann [120] produced ulcers in the jejunum by diverting the contents of the duodenum to the ileum and anastomosing the jejunum to the pyloric end of the stomach. Kapsinow [121] used a cholecystonephrostomy and ligation of the common bile duct to divert the bile and obtained subacute and chronic ulcers in the duodenum. Stuber [122] considered gastric ulcers to be tryptic in character and the result of the reflux of duodenal contents. Although supporting the theory of a disturbed balance between pepsin and antipepsin, Katzenstein [123] showed experimentally that living tissue is digested only by active gastric secretion. Hilarowicz and Mozolowski [124] found that the antipeptic action of the blood serum is due to its buffer content and concluded that there is no antipepsin. Kloster [125] demonstrated that the activity of gastric mucosa depends on the hydrogen ion concentration. Bálint [126] urged that because of finding abnormally high hydrogen ion concentration in the blood serum of patients with ulcers, a general alkalization of the entire body, and not alone of the gastric contents, should be attempted. He found the alkaline treatment also beneficial in other chronic processes such as ulcers of the leg. Miagawa, Murai and Terade,[127] working with isogastrotoxin, were able to produce ulcers; they believed that the direct action of resorbed cell components of the digestive mucous membrane and gastrotoxin and enterotoxin are the

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119. Smith, G. M.: An Experimental Study of the Relation of Bile to Ulceration of the Mucous Membrane of the Stomach, J. M. Research **30**:147, 1914.

120. Mann, F. C.: Production and Healing of Peptic Ulcer, Minnesota Med. **8**:638, 1925.

121. Kapsinow, R.: Experimental Production of Duodenal Ulcer by Exclusion of Bile from Intestine, Ann. Surg. **83**:614, 1926.

122. Stuber, B.: Zur Aetiologie des Ulcus ventriculi. Zugleich eine neue Theorie auf experimenteller Grundlage, München. med. Wchnschr. **61**:1265, 1914.

123. Katzenstein, M.: Ueber Entstehung und Behandlung des peptischen Magengeschwürs, Deutsche med. Wchnschr. **51**:1603, 1925.

124. Hilarowicz, H., and Mozolowski, W.: Ueber das Wesen des sogenannten Antipepsins des Blutes und über den diagnostischen Wert der Antipepsinuntersuchungen bei peptischem Magengeschwür, Zentralbl. f. Chir. **52**:2410, 1925.

125. Kloster, G. M.: Varying Hydrogen Ion Concentration Upon Rate of Action of Proteolytic Enzymes in Gastric Mucous Membrane, Proc. Soc. Exper. Biol. & Med. **24**:156, 1926.

126. Bálint, R.: Untersuchungen über die Pathogenese des Ulcus ventriculi, Wien. klin. Wchnschr. **39**:7, 1926.

127. Miagawa, Y.; Murai, H., and Terada, M.: An Experimental Study of the Cells of the Mucous Membrane of the Digestive Tract as Toxin or Irritant and Its Relation to Formation of Peptic Ulcer, Japan M. World **3**:123, 1923.

bases for the genesis of ulcers in the digestive tract. By experiment, Baggio [128] emphasized the importance of trauma such as may occur from food. Warren and Whipple [99] produced ulcers by roentgen rays. In his study of chronic gastric ulcer by this means, Wolfer [129] did not find hyperacidity or hypersecretion. In canine anaphylaxis, Manwaring, Beattie and McBride [130] found the most marked lesions in the duodenum. On the basis of local anaphylaxis to specific antigens, Shapiro and Ivy [131] produced acute ulcers in rabbits and dogs, many of which tended to become chronic, and found that in dogs the gastric reaction was most severe, and in rabbits, the skin reaction.

It will be noted that local interference in circulation plays the dominant rôle in most of the methods mentioned for producing ulcers. In discussing the blood supply of the stomach and duodenum, Reeves [132] pointed out the predisposition to thrombosis in the lesser curvature of the stomach and in the first inch of the duodenum, the latter having relatively fewer vessels than the rest of the duodenum. Müller and Heimberger [133] and Duschl [134] found that marked alteration was present in the capillaries in patients operated on for gastric and duodenal ulcers and that this vasoneurotic diathesis was also evident in the lips and skin. Fifteen years before, Strauss [135] had already emphasized the importance of predisposition and still considered that local ischemia from either relaxation or spasm accounted for an important part of the pathogenesis. Sennet [136] recalled Virchow's teaching that circulatory disturbance in the smallest arterioles was the basis of the genesis of gastric ulcer and further supported this view, developing the ways such changes may occur and the normal tendency to heal. Kaiser [137] said that the muscula-

128. Baggio, G.: Experimental Gastric Ulcer, Policlinico **33**:437, 1926; abstr., J. A. M. A. **87**:1871 (Nov. 27) 1927.

129. Wolfer, J. A.: Chronic Experimental Ulcer of the Stomach, J. A. M. A. **87**:725 (Sept. 5) 1926.

130. Manwaring, W. H.; Beattie, A. C., and McBride, R. W.: The Intestinal Lesion in Anaphylaxis, J. A. M. A. **80**:1437 (May 19) 1923.

131. Shapiro, P. F., and Ivy, A. C.: Experimental Production of Gastric Ulcer by Local Anaphylaxis, Arch. Int. Med. **38**:237 (Aug.) 1926.

132. Reeves, T. B.: Relation Between Ulcer and Arterial Supply of Stomach, Surg. Gynec. Obst. **30**:374, 1920.

133. Müller, O., and Heimberger, H.: Ueber die Entstehung des runden Magengschwürs, Deutsche Ztschr. f. Chir. **187**:33, 1924.

134. Duschl, L.: Anatomische Untersuchungen an Ulcusmägen, Deutsche Ztschr. f. Chir. **187**:55, 1924.

135. Strauss, H.: Geschwürsbereitschaft als Konstitutionswirkung, Arch. f. Verdauungskr. **37**:133, 1926.

136. Sennet, S. N.: Etiology of Gastric Ulcer, M. J. S. Africa **21**:268, 1926.

137. Kaiser, F. J.: Die Bedeutung mechanischer Momente für die Entstehung des Magengeschwürs. Die Ermüdungshypotonie und Ermüdungsatonie als Ulcusursache, Arch. f. klin. Chir. **134**:535, 1925.

ture of the stomach may become less elastic under reflex pain and exhaustion, the stretching of the stomach wall inviting nutritional disturbance and a consequent erosion. Mucci [138] held a loss of balance between the vagus and sympathetic nerves responsible for the ulcers. He said that this might be of emotional or toxic origin, or both. Monsarrat [139] believed that the alteration in gastric rhythm was the primary morbid condition. Morton [140] recently reemphasized the importance of the chemical and mechanical factors, as have so many others. The reported successful use of protein therapy by Pribram,[141] Holler [142] and Holler and Vecsler,[143] who used it to increase the tone of the visceral nerves and who believed that central nervous processes alone may induce ulcer, together with the not uncommon development of duodenal ulcers after extensive skin burns; the use of the roentgen ray to release local spastic conditions by Lenk,[144] the infrequency of recurrence after operations (Rivers and Eusterman [145]) and the recognized curative effects of nonsurgical methods such as those of White [146] and of the treatment of nervous indigestion by Alvarez,[147] all make it clear that infection is not alone the factor concerned. By directly infecting experimentally induced surgical ulcers with bacteria obtained from human gastric ulcer, Wilensky and Geist [148] did not find retardation in the healing time. It is true that a secondary infection by the blood stream might have had more effect.

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138. Mucci, D.: Origin of Gastric and Duodenal Ulcers, Arch. ital. di chir. **16**:193, 1926; abstr., J. A. M. A. **87**:1340 (Oct. 16) 1926.

139. Monsarrat, K. W.: Etiology of Gastric and Duodenal Ulceration, Brit. M. J. **1**:521, 1926.

140. Morton, C. B.: Experimental Chronic Gastric Ulcer, Ann. Surg. **87**: 207, 1927.

141. Pribram, B. O.: Parenterale Reizbehandlung des Magen-und Duodenalgeschwürs, Med. Klin. **18**:958, 1922.

142. Holler, H. G.: Klinisch-experimentelle Studien als Grundlage für Proteinkörpertherapie des Ulcus ventriculi und duodeni: I. Ulcus und Vagus, Arch. f. Verdauungskr. **29**:123, 1921-1922.

143. Holler, H. G., and Vecsler, J.: Ueber viszeralin Nerventonus und seine physiologischen und pathologischen Aüsserungen, mit besonderes Berucksichtigung der Verhältnisse im Magen und Duodenum, Arch. f. Verdauungskr. **31**:189, 1923.

144. Lenk, R.: Die Röntgentherapie der Ulkuskrankheit: II. Die Wirkungsweise der Röntgenstrahlen am Magen-Darmtrakt, Med. Klin. **21**:1001, 1925.

145. Rivers, A. B., and Eusterman, G. B.: Recurring Peptic Ulcer, Ann. Clin. Med. **4**:365, 1925.

146. White, F. W.: The Medical Treatment of Ulcer of the Stomach, Am. J. M. Sc. **173**:629, 1927.

147. Alvarez, W. C.: Treatment of Nervous Indigestion, J. A. M. A. **89**:440 (Aug. 6) 1927.

148. Wilensky, A. O., and Geist, S. H.: Experimental Study in Chronic Gastric Ulcer, J. A. M. A. **66**:1382 (April) 1916.

After this review of the many theories and experimental procedures to produce ulcers, it will be evident that the part played by bacteria must be carefully analyzed. Rosenow and many of the American investigators stressed the importance of the primary bacterial infection as the etiologic factor. The conditions favoring infection are certainly present in most of the predisposing causes I have listed. I have little doubt that infection frequently follows, as I believe it does in all the diseases discussed in this article. However, I feel that if progress is to be made in the appreciation of bacterial infections, the underlying condition, making possible the infection and the advance of the infection, must be emphasized, as has been done in tuberculosis and in other diseases.

Focal infection in other parts is a potential danger, and its association or etiologic relationship with gastric and duodenal ulcer has been noted, but not as frequently as in other conditions that will be discussed later. Rosenow and his school gave the tonsils and teeth as the most frequent association; Soper [149] included gastric ulcer in a list of systemic results after infections of the lower colon. In 30 patients with gastric or duodenal ulcer, Langstroth [150] found that 12 had alveolar abscesses also; 11, carious teeth or involved tonsils, and 1, chronic prostatitis, nearly 50 per cent having some associated infection. Hurst [151] was impressed with the frequent association of chronic appendicitis with such ulcers and thought the latter the primary condition. Le Noir, Richet and Jacquelin [152] noted the relative frequency of disease of the liver and kidney with chronic gastric ulcer, but only as complications of the latter condition. Of 522 patients with proved gastric ulcer, Smithies [153] listed 173 under his chronic and acute infection group. Zweig [154] called attention to the frequent coexistence of duodenal ulcer, cholecystitis and appendicitis, and considered them all due to infection from the intestines. Friedenwald and Morrison [155] reviewed the cases of 200 patients with gastric and duodenal ulcers and gave infection as the causative factor in 84. In 19 patients with chronic stomach trouble,

149. Soper, H. W.: The Mucosa of the Rectum and Sigmoid Colon as a Focus of Infection, Boston M. & S. J. **176**:766, 1917.

150. Langstroth, L.: The Incidence of Chronic Focal Infection in Chronic Diseases, Am. J. M. Sc. **155**:232, 1918.

151. Hurst, A. F.: New Views on Pathology, Diagnosis and Treatment of Gastric and Duodenal Ulcer, Brit. M. J. **1**:559, 1920.

152. Le Noir, P.; Richet, C., Jr., and Jacquelin, A.: Hépatites et néphrites secondaires à l'ulcère rond de l'estomac, Ann. de méd. **60**:225, 1921.

153. Smithies, F.: Significance of Etiologic Factors in the Treatment of Peptic Ulcer, J. A. M. A. **74**:1555 (June 5) 1920.

154. Zweig, W.: The Abdominal Triad, Arch. f. Verdauungskr. **27**:128, 1921; abstr. J. A. M. A. **76**:901 (March 26) 1921.

155. Friedenwald, J., and Morrison, T. H.: Etiology of Gastric and Duodenal Ulcers, South. M. J. **18**:315, 1925.

De Motte and Goldhorn [156] reported a cure in 8, relief in 5 and no relief in 6 after removal of dental foci of infection. I might add to this list the following: Bosányi [157] reported 2 cases of duodenal ulcers in young infants with extensive skin disease and related these to the ulcers following burns. Butka [158] reported a case of ruptured gastric ulcer in an infant, aged 6 days. In a personal communication, he said that there was no history of gastric ulcer in the mother. In 300 patients on whom operation was performed, Wilkie's [159] statistics showed 221 with ulcers only in the duodenum, 37 with ulcers only in the stomach and 42 with ulcers in both. This and other reports indicate that duodenal ulceration is a much more common condition than gastric ulceration.

A word may be said on the subject of ulcerative colitis, in which Bargen [160] found what he believed to be a specific organism with elective localizing power. Not much attention had been paid previously to the involvement of the colon in experimentally infected animals, and only a few comparative statistics are available. It is to be recalled that Ehrmann [161] related three of his four cases directly to dysentery and looked on the condition as a chronic form of this disease. In many cases of hemorrhagic colitis, Mayer [162] found atypical *B. coli* and strains of streptococci in the bowel; in these cases, a type of arthritis developed which was definitely different from articular rheumatism. Gale [163] reported the case of a patient with repeated perforations of the small intestines from a focus in either the teeth or the cutaneous furuncles, the Mayo Clinic favoring the first focus and he, the latter. In discussing Bargen's organism as the causative agent, Brown [164] was inclined to

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156. De Motte, R. J., and Goldhorn, E. G.: Results of Removal of Dental Focal Infections, J. Indust. Hyg. **11**:22, 1927.

157. Bosányi, A. Y.: Duodenal Ulcer in Children, Jahrb. f. Kinderh. **97**: 182, 1922; abstr. J. A. M. A. **78**:1500 (May 13) 1922.

158. Butka, H. E.: Ruptured Gastric Ulcer in Infancy, J. A. M. A. **89**:198 (July 16) 1927.

159. Wilkie, D. P. D.: Coincident Duodenal and Gastric Ulcer, Brit. M. J. **2**:469, 1926.

160. Bargen, J. A.: Experimental Studies on the Etiology of Chronic Ulcerative Colitis, J. A. M. A. **83**:332 (Aug. 2) 1924. Bargen, J. A., and Logan, A. H.: Etiology of Chronic Ulcerative Colitis, Arch. Int. Med. **36**:818 (Dec.) 1925. Bargen, J. A.: The Etiology and Treatment of Chronic Ulcerative Colitis, Am. J. Roentgenol. **16**:10, 1926.

161. Ehrmann, R.: Ueber die Colitis ulcerosa oder suppurativa, Berl. klin. Wchnschr. **53**:1285, 1916.

162. Mayer, A.: Ueber gehäuftes Auftreten von Gelenkerkrankungen nach Colitis haemorrhagica, Berl. klin. Wchnschr. **55**:378, 1918.

163. Gale, S. S.: Repeated Perforations of Small Intestine Due to Focal Infection, J. A. M. A. **79**:1047 (Sept. 23) 1922.

164. Brown, T. R.: Some Observations on Chronic Ulcerative Colitis, Ann. Clin. Med. **4**:425, 1925.

believe that the cause is not to be found in the presence of a definite and specific infective agent but rather in the absence of some protective substance or mechanism. He favored operation, as does Rienhoff.[165] Helmholz [166] believed in the specific organism as did Buie,[167] Wendkos [168] and others. Rubenstein [169] reported a patient treated with colon bacillus vaccine with permanent recovery.

APPENDIX

The anatomy of the appendix has given rise to much controversy, as has its function. Digby [47] considered it part of the subepithelial lymphoid defense mechanism. He emphasized the following points: The cecum is relatively small in man, the cat and the dog and is largest in the rabbit; in the dog and the cat, the appendix is represented by a bulging mass of lymphoid tissue at the apex of the cecum; a well developed appendix occurs in the rabbit and in man. The different conditions associated with these anatomic variations should be considered in experiments on animals. Crypts are present in the human appendix, much as they are in the tonsil, and the infection may start here with the development of local ulcers or from an infection of the blood stream in the wall. In any case, closure by stricture following inflammation complicates the process. Landsdown and Williamson [170] believed that there is an underlying common cause for appendicitis and gastric and duodenal ulcer, and that sepsis and chronic ulceration are secondary features or sequelae.

Appendicitis as a disease was apparently first recognized by Heister in 1753.[171] Many attempts have been made to produce the condition by various surgical procedures, and they will not be reviewed here. Poynton and Paine [172] produced appendicitis along with arthritis and mucous

165. Rienhoff, W. F.: The Surgical Treatment of Chronic Ulcerative Colitis by Ileo-Sigmoidostomy, Ann. Clin. Med. **4**:430, 1925.

166. Helmholz, H. F.: Chronic Ulcerative Colitis in Childhood, New York State J. Med. **26**:46, 1926.

167. Buie, L. A.: Chronic Ulcerative Colitis, J. A. M. A. **87**:1271 (Oct. 16) 1926.

168. Wendkos, S.: Chronic Ulcerative Colitis—Two Cases Treated with Bargen's Serum, M. J. & Record **125**:379, 1927.

169. Rubinstein, J.: Treatment of Chronic Ulcerous Colitis by Colon Bacillus Autovaccine, Arch. f. Verdauungskr. **39**:117, 1926; abstr. J. A. M. A. **88**:613 (Feb. 19) 1927.

170. Lansdown, R. G. P., and Williamson, G. S.: Etiology of Appendicitis, Gastric Ulcer and Allied Conditions, Brit. J. Surg. **6**:350, 1914.

171. Mackall, L. A.: The Earliest Recognition of Appendicitis—Again, Correspondence, J. A. M. A. **80**:572 (Feb. 24) 1923. Ashhurst, A. P. C.: Correspondence, ibid. **80**:789 (March 17) 1923.

172. Poynton, F. J., and Paine, A.: A Further Contribution to the Study of Rheumatism, the Experimental Production of Appendicitis by the Intravenous Inoculation of the Diplococcus, Proc. Roy. Soc. London **5**:18 (path. sect.), 1911-1912.

colitis in four of twenty-four rabbits injected intravenously with a streptococcus obtained from the joint of a patient with acute articular rheumatism and referred to similar results reported by Adrian ten years previously. Ghon and Namba [173] reported finding gross lesions in the appendixes of thirty-seven of fifty-five normal rabbits; they found that in the remaining eighteen a number showed microscopic changes. They therefore questioned the results of Tedesco, Adrian and others. Stoeber and Dahl [174] injected pneumococci in the region of the tonsil of eight rabbits on six succeeding days and obtained infections in the lymph follicles of the appendix. Rosenow [175] also was successful in obtaining localization in the appendix of a large number of animals, principally rabbits, using streptococci and other bacteria from the tonsils, appendixes and other sources.

The bacteriology of appendicitis is extensive. Perrone [176] gave a good review up to 1905. Haim [177] considered streptococci to be the chief cause in children and colon bacillus in adults. Isabolinsky [178] studied fifty cases and concluded that many different bacteria may be the cause. Brown and Cade [179] obtained *Streptococcus fecalis* from the blood of a patient with acute appendicitis. Other studies have been made by Bagger and Mikkelsen,[180] Warren [181] and many others. All types of bacteria have been found, and it is difficult to determine the etiologic importance of any one group. However, the evidence is generally considered as pointing to the streptococcus group as the most dangerous.

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173. Ghon, A., and Namba, K.: Zur Frage die Genese der Appendicitis, Beitr. z. path. Anat. u. z. allg. Pathol. **52**:130, 1912.

174. Stoeber, H., and Dahl, W.: Experimentelle hämatogene Infektion der Lymphfollikel des Appendix, Mitt. a. d. Grenzgeb. d. med. u. Chir. **24**:645, 1912.

175. Rosenow, E. C.: Bacteriology of Appendicitis and Its Production by Intravenous Injection of Streptococci and Colon Bacilli, J. Infect. Dis. **16**:240, 1915. Rosenow, E. C., and Dunlap, S. I.: An Epidemic of Appendicitis and Parotitis, Probably Due to Streptococci Contained in Dairy Products, ibid. **18**:383, 1916.

176. Perrone: Contribution a l'étude de la bactériologie de l'appendicite, Ann. de l'inst. Pasteur **19**:367, 1905.

177. Haim, E.: Zur Appendicitisfrage, Zentralbl. f. Chir. **2**:33, 1907; Zur Frage der bakteriellen und insbesondere der durch Streptokokken hervorgerufenen Appendicitis, Arch. f. klin. Chir. **82**:360, 1907.

178. Isabolinsky, M.: Zur Bakteriologie der Appendicitis, Centralbl. f. Bakteriol. **73**:488, 1914.

179. Brown, H. H., and Cade, H. M.: Postoperative Mortality of Appendicitis, Lancet **1**:118, 1921.

180. Bagger and Mikkelsen: Bacteriology of Appendicitis, Hospitalstidende **67**:284, 1924; abstr., J. A. M. A. **83**:314 (July 26) 1924.

181. Warren, S.: The Etiology of Acute Appendicitis, Am. J. Path. **1**:241, 1925.

Many investigators, such as Weber,[182] have suggested a relationship between tonsillitis and appendicitis. Watson-Williams [183] found that infections of the accessory nasal sinuses were often associated. Mayo [184] pointed out its relation as a focus of disease to other abdominal diseases, and I have referred to a number of other similar reports.

GALLBLADDER

The anatomy and the interrelationships of the gallbladder to the liver and other organs have been well studied (Kodama [185]). The gallbladder is normally sterile, as Toida [186] has shown, but bacteria are excreted or leave the circulation during a bacteremia, not infrequently with the bile, as is the case in typhoid fever, and a localization in the gallbladder is common. Welch [187] found this with *B. typhosus,* and the early work of Trambusti and Maffucci,[188] Bernice and Scagliosi [189] and many others emphasizes the importance of this route of bacterial elimination from the body.

The well known bactericidal action of bile on various bacteria has been extensively studied, and a brief review of this topic has been given by Stone.[190] In her work she found that bile of the rabbit had a bactericidal effect on certain strains of streptococci but that it was ineffective toward others. All strains of *Streptococcus pyogenes* (27) being killed, only one of eighteen strains of *Streptococcus infrequens* (a mannit fermenter), none of the nonhemolytic streptococci (24) and of the latter, sixteen were listed as *Streptococcus fecalis,* and all but four fermented

182. Weber, H.: Zur Kritik der Beziehungen der Angina tonsillaris zur Entzündung des Wurmfortsatzes, München. med. Wchnschr. **52**:41, 1902.

183. Watson-Williams, P.: Nasal Sinus Infection Causal Factor in Appendicitis, Practitioner **106**:229, 1921.

184. Mayo, C. H.: The Appendix in Relation to, or as the Cause of, Other Abdominal Diseases, J. A. M. A. **83**:592 (Aug. 23) 1924.

185. Kodama, S.: Lymphatics of Extrahepatic Biliary Passages, Surg. Gynec. Obst. **43**:140, 1926.

186. Toida, R.: Zur Frage von der Sterilität der Galle unter normalen Verhältnissen und über ihre bakterizide Wirkung auf pathogene Bakterien, Arch. f. klin. Chir. **103**:407, 1914.

187. Welch, W. H.: Additional Note Concerning the Intravenous Inoculation of Bacillus Typhi Abdominalis; Its Survival in the Gall Bladder, Bull. Johns Hopkins Hosp. **2**:121, 1891; Papers and Addresses, Bacteriology **2**:332, 1920; Experimental Production of Typhoid-Bacillus Carriers: Bacteria in Gall Stones, Bull. Johns Hopkins Hosp. **26**:32, 1915; Papers and Addresses, Bacteriology **2**:335, 1920.

188. Trambusti, A., and Maffucci, A.: Sull'eliminazione del virus dall' organismo Animale, Riv. internat. di med. e. chir. **3**:505, 1886.

189. Bernice, B., and Scagliosi, G.: Ueber die Ausscheidung des Bacterien aus dem Organism, Deutsche med. Wchnschr. **18**:761, 1892.

190. Stone, R. L.: The Bactericidal Action of Rabbit Bile on Certain Strains of Streptococci, Am. J. Hyg. **21**:67, 1922.

mannit. This work, together with that already quoted,[191] makes it appear logical that fecal streptococci, having passed through the duodenum and survived the action of bile, are usually resistant to bile. Further, Stone reported that various strains of *Streptococcus pyogenes* killed by small amounts of bile from the rabbit were unaffected by any concentration of bile from the cow, sheep, pig, dog, cat, guinea-pig, turtle or from man. Details of this most important part of Stone's work were unfortunately not given, but her general results showed clearly that, in experiments on animals, this variation in types of bile must be carefully considered. The effect of bile on the local bacterial flora is, of course, most important.

A great many reports have been made concerning the bacteriology of cholecystitis and cholelithiasis, and only a few will be mentioned. Rosenow's work, incorporated in his general articles, will be described later. Gilbert and Lippmann [192] found enterococcus, streptococcus and other types. Funke [193] studied 102 calculi and found a variety of bacteria. Moon [194] considered that the colon bacteria are the most important and that they enter through the mucosa. He said that streptococci are not concerned in the etiology of gallstones. Other studies have been reported by Brown,[195] who stressed particularly the streptococci and their effect in rabbits; by Richey [196] and Drennan [197] and by Johnson,[198] who found bacteria in less than a third of his cases; by Hansen,[199] who found the bile usually sterile and the gallbladder healthy in early cholelithiasis and believed that infections were secondary; by von Hedry [200] and by Judd, Mentzer and Parkhill,[201] who particularly

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191. Footnotes 13, 14 and 15.

192. Gilbert, A., and Lippmann, A.: Bactériologie des cholecystites, Compt. rend. Soc. de biol. **54**:1189, 1902.

193. Funke, J.: Cholelithiasis; the Aetiology and Bacteriological Study of 102 Calculi, New York M. J. **84**:1077, 1906.

194. Moon, S. B.: Diseases of Biliary Tract, Society Transactions, J. A. M. A. **65**:2193 (Dec. 18) 1915.

195. Brown, R. O.: A Study on the Etiology of Cholecystitis and Its Production by the Injection of Streptococci, Arch. Int. Med. **23**:185 (Feb.) 1919.

196. Richey, De W. G.: The Bacteriology of Human Cystic Bile, Penn. M. J. **26**:4, 1922.

197. Drennan, J. G.: Bacteriologic Study of Fluid Contents of 100 Gall Bladders Removed at Operation, Ann. Surg. **76**:482, 1922.

198. Johnson, W. O.: One Hundred Consecutive Cholecystectomies, Am. J. M. Sc. **170**:181, 1925.

199. Hansen, S.: The Bacteriology of the Bile, Hospitalstidende **69**:289, 1926; abstr., J. A. M. A. **87**:136 (July 10) 1926.

200. Von Hedry, N.: Beiträge zur Bakteriologie der Gallenblase auf Grund der Untersuchung von 100 operierten Fällen, Beitr. z. klin. Chir. **135**:665, 1926.

201. Judd, E. S.; Mentzer, S. H., and Parkhill, E.: A Bacteriologic Study of Gall Bladders Removed by Operation, Am. J. M. Sc. **173**:16, 1927.

emphasized the importance of making cultures from the wall of the bladder as Rosenow had. Kusunoki [202] demonstrated the passage of bacteria that had been injected into the portal circulation into the bile and general circulation. The method for determining the bacterial flora of the bile by using the duodenal tube has been shown by Alvarez, Meyer, Rusk, Taylor and Easton [203] to be fundamentally unsound, and they pointed out that particularly in chronic cholecystitis the infectious process is localized both in the walls and throughout the liver; Boardman [204] has also demonstrated the chances of error in this method through contamination by the bacteria in the saliva. Huntemüller [205] particularly studied the bacteriology of the bile ducts and the principles underlying the presence of bacteria. The mechanism of infection of the gallbladder has been reported by Meyer, Neilson and Feusier.[206] Experimental cholecystitis was produced by Harkins [207] by direct implantation of various bacteria into the gallbladder. After intravenous injection of *Streptococcus hemolyticus, Streptococcus viridans* and *Enterococcus,* Meyer and Löwenberg [208] found that only the latter showed a predilection for the gallbladder. As I have indicated, this organism is highly resistant to bile, and here one finds a reason for a certain type of "elective localization."

The etiology of cholelithiasis is in itself too large a topic to be more than briefly discussed here. Hansen,[199] Rovsing [209] and many others considered the gallstones the cause and not the result of infection. Rous

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202. Kusunoki, M.: Action of Liver on Bacteria in the Blood, Mitt. a. d. med. Fak. Univ. Kyushu. **8**:265, 1924; abstr., J. A. M. A. **84**:1012 (March 28) 1925.

203. Alvarez, W. C.: Is the Meltzer-Lyon Technic for the Diagnosis and Treatment of Gall Bladder Disease an Asset or a Liability? California State J. Med. **20**:262, 1922; The Diagnosis and Treatment of Gall Bladder Disease, ibid. **20**:299, 1922. Alvarez, W. C.; Meyer, K. F.; Rusk, G. Y.; Taylor, F. B., and Easton, J.: Present Day Problems in Regard to Gallbladder Infections: A Statistical Inquiry, J. A. M. A. **81**:974 (Sept. 22) 1923.

204. Boardman, W. W.: Bacteriologic Findings in Lyon-Meltzer Test, Am. J. M. Sc. **167**:847, 1924.

205. Huntemüller: Die entzündlichen Erkrankungen der Gallenwege von Standpunkte des Bacteriologen, Klin. Wchnschr. **3**:349, 1924.

206. Meyer, K. F.; Neilson, N. M., and Feusier, M. L.: Mechanism of Gall Bladder Infections in Laboratory Animals, J. Infect. Dis. **28**:456, 1921.

207. Harkins, M. J.: Pneumococcolytic Activity of Bile from Experimental Bacterial Cholecystitis of Rabbits, J. Lab. & Clin. Med. **10**:716, 1925.

208. Meyer, K., and Löwenberg, W.: Experimentelle Untersuchungen zur Enterokokkeninfektion der Gallenblase: Ein Beitrag zum Problem der elektiven Lokalisation von Krankheitserregern, Klin. Wchnschr. **5**:989, 1926.

209. Rovsing, T.: Gallstones Cause, Not Result of Infection, Acta chir. scandinav. **56**:207, 1923; abstr., J. A. M. A. **81**:2072 (Dec. 15) 1923.

and his associates [210] were able to produce gallstones in the absence of infection, and it is generally believed that an upset in the cholesterol metabolism is at the bottom of this production. Although he emphasized the great importance of hypercholesterolemia, Moynihan [211] believed that infection was also necessary and that it came from various foci in the accessory sinuses, the teeth, the urinary or digestive tract or other sites. The colon bacillus was the commonest observation in his report, having been present in 48 of 100 consecutive cases. Streptococci were found in only eight cases. Moynihan presented an excellent discussion of the whole problem.

McMaster, Brown and Rous [212] found that intercurrent disease lessened the amount of bile flow almost to cessation, and in this they agreed with Rovsing.[213] McMaster and Elman [214] studied the effect of infections of the biliary tract, and reported that these infections produced urobilin from the bilirubin of the bile. Therefore, a great deal of evidence pointing to the importance of infection in these conditions presents itself. There is, however, only a meager suggestion of any specific micro-organism being held responsible.

The relationship between infectious processes in the gallbladder and those in other parts of the body has been repeatedly stressed, in regard to the gallbladder being a primary focus of infection as well as a site of secondary infection. Langstroth [150] had four patients with chronic disease of the gallbladder; two of the cases were associated with alveolar abscesses, and one patient had infected tonsils and one, a chronic prostatitis. He believed, however, that chronic infections in the teeth were responsible for the recurrent attacks of cholecystitis in most cases. Many more reports of the same character, suggesting infection from the respiratory tract, might be quoted. In contrast with this, one finds the relation of these infections to other more or less local conditions in the abdominal cavity so familiar to all surgeons and clinicians. Harris [215]

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210. Rous, P.; McMaster, P. D., and Brown, G. O.: The Experimental Production of Gall Stones in Dogs in the Absence of Infection, Stasis, and Gall Bladder Influence Upon the Bile, Proc. Soc. Exper. Biol. & Med. **20**:128, 1922. Rous, P.; McMaster, P. D., and Drury, D. R.: The Genesis of Gall Stones in the Dog, ibid. **20**:315, 1923.

211. Moynihan, B.: Some Aspects of Cholelithiasis, Brit. M. J. **1**:393, 1925.

212. McMaster, P. D.; Brown, G. O., and Rous, P.: Studies on the Total Bile, J. Exper. Med. **37**:395, 1923.

213. Rovsing, T.: Gallstones as a Result of Transient Inspissation of the Bile, Hospitalstidende **58**:249, 1915; abstr., J. A. M. A. **64**:1460 (April 24) 1915.

214. McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology: VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, J. Exper. Med. **43**:753, 1926.

215. Harris, S.: Pancreatitis as Related to Gastro-Intestinal and Gallbladder Infection, J. A. M. A. **81**:1496 (Nov. 3) 1923.

showed the relation to pancreatitis, Lichty and Woods,[216] to glycosuria and Soper,[217] to infections of the gastro-intestinal tract. By repeated intravenous injections of *Streptococcus hemolyticus* and *B. typhosus*, Ricen [218] was able to obtain only diabetic symptoms in animals with intact gallbladders and considered the primary infection to be in the gallbladder, which secondarily affected the pancreas.

PANCREAS

From what has already been said, it is evident that the pancreas is not spared in this type of infection. After Schwartz, Heiman and Mahnken [219] reported the sugar content of the blood in a series of diseases of the skin such as acne and sycosis and suggested a relation between the pilosebaceous follicles and an excess of blood sugar, and after Thalhimer [220] described the condition of his patient who had furunculosis associated with high blood sugar, much attention has been given to blood sugar under this and similar conditions. It is not at all clear whether this increase in blood sugar is the result of coincident pancreatic deficiency or of change in the metabolism in other parts of the body, but the latter hypothesis seems the more probable. In studying this problem about five years ago, Miller and I [221] fed a high carbohydrate diet to a number of rabbits. These animals soon showed a blood sugar content well above that of the controls, with the exception of one, which had developed a submaxillary abscess from an infection with *B. leptisepticus*. This abscess was opened and curetted and promptly healed, and the blood sugar rose to about the same amount as in the rabbits fed on sugar. These animals and a series of guinea-pigs fed on a similar diet all developed abscesses on subcutaneous injection of *Staphylococcus aureus*, while the controls showed only a passing reaction with the dosage used. The interesting question was, Why did the spontaneously infected rabbit not respond to the feeding like the others? Handmann [222] investigated the cause of the lowered resistance

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216. Lichty, J. A., and Woods, J. O.: The Significance of Glycosuria in Gall Bladder and Duct Diseases, Am. J. M. Sc. **167**:1, 1924.

217. Soper, H. W.: Relationship Between Disease of the Gall Bladder and Infection in the Gastro-Intestinal Tract, Ann. Clin. Med. **4**:422, 1925.

218. Ricen, L.: Cholecystitis and Diabetes, Northwest Med. **25**:101, 1926; abstr., J. A. M. A. **86**:1801 (June 5) 1926.

219. Schwartz, H. J.; Heiman, W. J., and Mahnken, H. C.: Sugar Content of the Blood in Various Skin Diseases, J. Cutan. Dis. **34**:159, 1916.

220. Thalhimer, W.: The Relationship of High Blood Sugar to Furunculosis, J. A. M. A. **76**:295 (Jan. 29) 1921.

221. Holman, W. L., and Miller, R. E.: Relation of High Blood Sugar Content to Certain Bacterial Infections, unreported experiments.

222. Handmann, E.: Resistenz des Diabetikers gegen Infektionen, Deutsches Arch. f. klin. Med. **52**:1, 1911.

of diabetic patients to infection and concluded that since from 0.5 to 1 per cent of sugar added to blood did not favor the growth of staphylococci nor change the bactericidal character of the blood, the reason was to be sought in cellular changes. Blodgett [223] believed that in a number of patients who had the acute pancreatic form of diabetes the condition was due to an infection of the pancreas following an infection of the tonsils and reported four cases. Allen [224] studied the effect of cold on the function of the pancreas, as a rule, producing hyperglycemia and sometimes glycosuria; although he distinguished this effect from that producing diabetes, he felt that cold may increase the burden on the pancreatic function by increasing metabolism. John [225] found that a "cold" in a diabetic patient raised the blood sugar content and that in young patients it tended to lower the carbohydrate tolerance permanently. Visher [226] believed that some cases of diabetes are due to pancreatitis and cited five cases secondary to abdominal and rectal infections. He thought that the infection reached the pancreas by way of the lymphatics. Holcomb [227] supported the theory of the infectious origin of diabetes. Richardson [228] stressed the importance of focal infection in at least complicating the progress and cure of the disease. Garrett [229] discussed the rôle played by mumps, as did Gundersen,[230] and they both gave a considerable bibliography on this relationship.

Hirsch [231] studied experimentally the effect of bacterial injections in producing hyperglycemia and thought that it depended on the extent of the diminution of the alkali reserve. From similar experiments, Levine and Kolars [232] found that they could divide their bacteria into three groups: (1) Those causing an increase (colon-dysentery-paratyphoid A group, staphylococcus and pneumococcus I); (2) those not causing any

223. Blodgett, S. H.: Diabetes (Pancreatic) Caused by Infection of Tonsils, Penn. M. J. **24**:407, 1921.

224. Allen, F. M.: Influence of Cold on Function of Pancreas, Am. J. Physiol. **54**:425, 1921.

225. John, H. J.: Insulin in Diabetes, M. J. & Record **119**:229, 1924.

226. Visher, J. W.: Relation of Abdominal and Rectal Infections to the Pathogenesis of Diabetes Mellitus, Am. J. M. Sc. **171**:836, 1926.

227. Holcomb, B.: Influence of Focal Infections on Diabetes, J. Lab. & Clin. Med. **11**:874, 1926.

228. Richardson, R.: Influence of Focal Infection on Diabetes, Atlantic M. J. **30**:232, 1927.

229. Garrett, F. D.: Chronic Pancreatitis: Case Reports and Rôle of Mumps and Measles, Southwestern M. J. **11**:172, 1927.

230. Gundersen, E.: Is Diabetes of Infectious Origin? J. Infect. Dis. **41**: 197, 1927.

231. Hirsh, E. F.: Changes in the Alkali Reserve, Sugar Concentration and Leukocytes of the Blood in Experimental Medicine, J. Infect. Dis. **29**:40, 1921.

232. Levine, V. E., and Kolars, J. J.: The Effect on Blood Sugar of Injections of Bacteria, Proc. Soc. Exper. Biol. & Med. **24**:36, 1926.

change (in which are *Streptococcus viridans, B. typhosus* and others); (3) those causing a decrease (*Streptococcus hemolyticus* alone). Menten and Manning [233] demonstrated that rabbits under adverse environmental conditions developed a hyperglycemia, coincident with the presence of paratyphoid bacilli in their organs, as well as striking changes in the islets of Langerhans. Injections of killed or living organisms gave similar pathologic conditions. Rosenow,[106] whose work will be discussed later, included the pancreas in the organs attacked by elective localizing streptococci.

KIDNEYS

A careful study of the anatomy of the kidney has been made by Gross [234] and more recently by Richards [235] and MacCallum.[236] The importance of the blood supply to the occurrence of infection is obvious. The circulation is primarily a glomerular one. The fact that the wall of the capillaries in the glomerulus is peculiar in structure, as shown by Merkel,[237] the importance of the slowing of the blood flow as determining the place of localization of infection as first emphasized by Wyssokowitsch,[238] the effect of pressure, increased by the unyielding glomerular capsule on the circulation (Kuczynski [67]), all help to explain the reason for the frequent finding of evidence of infection in the kidneys after intravenous injection when the liver, spleen and other organs have overcome the bacteria and have returned to a relatively normal state. Kuczynski [67] also pointed out the difference in the anatomic structure of the kidney in different animals and the variability in reaction as a result of individual differences. Fahr [239] concluded from his studies that the swelling of the endothelial cells of the glomeruli was the primary lesion in glomerulonephritis, and this has been the view generally held since the

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233. Menten, M. L., and Manning, H. M.: Blood Sugar Studies on Rabbits Infected with Organisms of the Enteritidis—Paratyphoid B. Group, J. M. Research **40**:675, 1924; Relationship of Enteritidis-Paratyphoid B. Infections to Hyperglycemia in Rabbits, J. Infect. Dis. **37**:400, 1925.

234. Gross, L.: Studies on the Circulation of the Kidney in Relation to Architecture and Function of the Organ in Health and Disease, J. M. Research **36**:327, 1917; ibid. **38**:379, 1918.

235. Richards, A. N., and Schmidt, C. F.: The Glomerular Circulation in Frogs' Kidney; Action of Epinephrin and Various Other Substances on It, Am. J. Physiol. **71**:178, 1924.

236. MacCallum, D. B.: Arterial Blood Supply of Mammalian Kidney, Am. J. Anat. **38**:153, 1926.

237. Merkel: Anatomie **4**:141, 1915; quoted from Kuczynski (footnote 67).

238. Wyssokowitsch, W.: Ueber die Schicksale der in's Blut injizierten Mikroorganismen im Körper der Warmblüter, Ztschr. f. Hyg. u. Infectionskrankh. **1**:3, 1886.

239. Fahr, T.: Zur Pathogenese der akuten Glomerrulonephritis, Deutsche med. Wchnschr. **52**:735, 1926.

time of Wyssokowitsch.[238] Arataki [240] observed that the formation of glomeruli in the rat continued throughout the first hundred days of life. Smith, Morse and Jones [240] showed that the divergent results in feeding experiments largely depended on this and, of course, that this would also affect the results in bacterial and other experiments.

The experimental production of nephritis has been attempted by so many different methods that I will confine myself to certain of these which have a bearing on the problem. The discovery of spontaneous nephritis in animals by Ophüls and McCoy,[241] Ophüls,[242] Klotz,[243] McGowan,[244] Bell and Hartzell,[245] Bloomfield,[246] Kuczynski,[67] Leiter [247] and others has not so much discounted the results of all experimental work as it has shown that animals are susceptible to such diseases under natural conditions. Experimental work depends on controls and statistics. The effect of cold on the kidney has been tested by a number of workers. Siegel [248] found that cold alone would cause nephritis in dogs and remarked that in winter many dogs suffered from irritation of the kidney. Cicconardi [249] brought about changes in the kidney by cold but did not consider that cold by itself would produce a true nephritis. Gaisbock [250] produced nephritis of the glomerulartubular type by cold; by simultaneous chilling and injection of streptococci, he produced an acute interstitial nephritis. In his experiments, Forssner [251] used a

240. Arataki, M.: Am. J. Anat. **36**:399, 1926; quoted from Smith, A. H.; Morse, T. S., and Jones, M. H.: Diet and Tissue Growth. Relation of Age to Renal Injury on Diet Rich in Protein, Proc. Soc. Exper. Biol. & Med. **24**:746, 1927.

241. Ophüls, W., and McCoy, G. W.: Spontaneous Nephritis in Wild Rats, J. M. Research **26**:249, 1912.

242. Ophüls, W.: Some Interesting Points in Regard to Experimental Chronic Nephritis, J. M. Research **18**:497, 1908.

243. Klotz, O.: Experimental Bacterial Interstitial Nephritis, Tr. A. Am. Phys. **29**:49, 1914.

244. McGowan, J. P.: "Spontaneous Nephritis" in Rabbits and Its Possible Relationship to Coccidiosis, Proc. Path. Soc., J. Path. & Bact. **23**:117, 1919.

245. Bell, E. T., and Hartzell, T. B.: Spontaneous Nephritis in Rabbits and Its Relation to Chronic Nephritis in Man, J. Infect. Dis. **24**:628, 1919.

246. Bloomfield, A. L.: The Relationship of Spontaneous Nephritis of Rabbits to Experimental Lesions, Bull. Johns Hopkins Hosp. **30**:121, 1919.

247. Leiter, L.: Experimental Chronic Glomerulonephritis, Arch. Int. Med. **33**:611 (May) 1924.

248. Siegel: Abkühlung als Krankheitsursache, Deutsche med. Wchnschr. **34**: 454, 1908.

249. Cicconardi, G.: On the Alterations Caused in the Kidneys by Cold, Arch. per le sc. méd. **43**:247, 1920; abstr. Med. Sciences, Abstracts & Reviews **5**:260, 1921-1922.

250. Gaisbock, F.: Experimentelle und anatomische Untersuchungen zur Frage der Kältenephritis, Wien. Arch. f. inn. Med. **3**:1, 1922.

251. Forssner, G.: Renale Lokalisation nach Intravenöse Infektionen mit einer dem Nierengewebe experimentell angepassten Streptokokkenkultur, Nord. med. Ark. **2**:1, 1902.

hemolytic streptococcus from an axillary abscess. He grew the organism in extracts from the kidney and in the whole kidney of infected rabbits and found that when it had adapted itself and gave luxuriant growth in the extract, cultures in this medium, injected intravenously into rabbits, tended to locate more in the kidney than in the liver or the spleen depending on the day the animals were killed. This was determined by counting the number of streptococci isolated from weighed amounts of these organs. In table 8 he showed that 58 per cent, or eighteen of his thirty-one rabbits showed such localization. In six of these, abscess-like foci were found in the kidney and in four others, acute interstitial changes. Three of the rabbits showing abscess-like foci were killed in two days; one with interstitial changes, in one day and one in two days, which makes it probable that there were spontaneous lesions in certain of his animals and that at the site of such lesions the acute process developed, which would certainly increase the bacterial count. The extract from the kidney added to cultures of this streptococcus before it had become adapted did not cause the streptococcus to locate predominantly in the kidneys. It is to be noted that the extract from the kidney in which the adapted streptococcus was growing luxuriantly was not tested after filtration for its effect on the kidneys. A toxin may have been produced or the streptococcus may have split the proteins present, as Wollman, Urbain and Ostrowsky [252] have demonstrated, and these split proteins may have damaged the kidneys. This report of Forssner's is probably the basis for the elective localization theory and will be referred to later.

Emerson [253] reviewed the subject of experimental nephritis to 1908. Le Count and Jackson [254] used streptococci, mostly hemolytic, and obtained various grades of nephritis in rabbits. Klotz [243] used cultures of *Streptococcus viridans* and obtained acute and chronic glomerular and chronic interstitial nephritis. In attempting to produce iritis, Stoddard and Woods [255] injected staphylococci and streptococci and found changes in the kidney. Helmholz and Beeler [256] did not find any specific tendency for colon bacilli obtained from patients with pyelocystitis to locate in

252. Wollman, E.; Urbain, A., and Ostrowsky, J.: Application de la technique au B. coli á l'étude du pouvoir protéolytique des streptocoques, Compt. rend. Soc. de biol. **87**:1138, 1922.

253. Emerson, H.: An Experimental and Critical Study of the Etiology of Chronic Nephritis, Arch. Int. Med. **1**:484 (June) 1908.

254. Le Count, E. R., and Jackson, L.: The Renal Changes in Rabbits Inoculated with Streptococci, J. Infect. Dis. **15**:389, 1914.

255. Stoddard, J. L., and Woods, A. C.: A Note on Experimental Nephropathy from Some Bacterial Poisons, J. M. Research **34**:343, 1916.

256. Helmholz, H. F., and Beeler, C.: Focal Lesions Produced in the Rabbit by Colon Bacilli Isolated from Pyelocystitis Cases, Am. J. Dis. Child. **14**:5 (July) 1917.

the kidney. Faber and Murray [257] failed to produce typical glomerulonephritis with staphylococci, streptococci or colon bacilli and opposed the theory that it is due to bacteriolysis of streptococci or to allergy. Mayo [258] reviewed the subject of hematogenous infections of the kidney to 1919. Kuczynski [67] fully discussed the various theories. Kinsella and Sherburne [259] produced endocarditis after injuring the aortic valve and injecting *Streptococcus viridans,* and later found glomerular lesions in the kidney. Other examples of similar results will be referred to in the part of this article which concerns the heart. Takenomata [260] considered that most cases of nephritis were due to streptococci. He used a toxin of a hemolytic streptococcus and found that active immunity made the kidney hypersensitive, while passive immunity gave protection. His experiments showed a mixture of glomerulonephritis and nephrosis. Leiter [247] found a "spontaneous" nephritis in 40 per cent of his control rabbits, and the same lesion was obtained in 72 of 133 rabbits used in his experiments. He therefore questioned the results of all previous workers. Bell, Clawson and Hartzell [261] produced the same "spontaneous" type of nephritis (lymphocytic interstitial) in a number of rabbits with streptococci from human sources. They succeeded in obtaining a glomerulonephritis of the human type in a monkey. In an extensive study of nephropathies, Dake [262] reviewed the literature of the experiments that had been done with pneumococci, streptococci, staphylococci and their toxins, and reported his own results. He found that hypersensitivity was developed by repeated doses of the cocci. Duval and Hibbard [263] were successful with the toxic principle of the scarlatinal streptococcus obtained from the peritoneal fluid of passively immunized animals after injection with the streptococcus. These filtrates from the peritoneal cavity produced typical glomerulonephritis in rabbits. From

257. Faber, H. K., and Murray, V.: An Attempt to Produce Glomerulonephritis by Repeated Injections of Bacteria, J. Exper. Med. **26**:707, 1917.

258. Mayo, W. J.: Hematogenous Infections of the Kidney, J. A. M. A. **73**: 1023 (Oct. 4) 1919.

259. Kinsella, R. A., and Sherburne, C. C.: Experimental Production of Streptococcus Endocarditis with Glomerular Nephritis, Proc. Soc. Exper. Biol. & Med. **20**:252, 1923.

260. Takenomata, N.: Experimenteller Beitrag zur Pathogenese der Streptokokkennephritis, Mitt. ü. allg. Pathol. u. path. Anat. **2**:15, 1923.

261. Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: Experimental Glomerulonephritis, Am. J. Path. **1**:247, 1925.

262. Dake, T.: Beiträge zur Kenntnis der akuten Nephropathien durch Baketerientoxine: III. Mitteilung Akute Nephropathien durch Kokkenarten, Mitt. ü. allg. Pathol. u. path. Anat. **2**:495, 1926.

263. Duval, C. W., and Hibbard, R. J.: Experimental Production of Acute Glomerulonephritis, J. A. M. A. **87**:898 (Sept. 18) 1926; Experimental Glomerulonephritis Induced in Rabbits with the Endotoxic Principle of Streptococcus Scarlatinae, J. Exper. Med. **44**:567, 1926.

this review, it is clear that the disease picture of one type of disease of the kidney comparable to that in man is difficult and is infrequently produced in experimental animals. Bumpus and Meisser,[264] Rosenow and Meisser [265] and Haden [266] attempted to prove that various diseases of the kidney are the result of infections with bacteria that have elective localizing powers.

The dangerous effect of a high protein diet was discussed by Squier and Newburgh,[267] Evans and Risley,[268] Newburgh and Clarkson,[269] Newburgh, Marsh, Clarkson and Curtis [270] and Newburgh,[271] the latter did not consider that foci of infection have anything to do with at least the chronic parenchymatous type of nephritis. The work of Peters and Bulger [272] on dietary control was an important contribution to this problem. Jackson [273] showed the development of nephritis in rats kept on a diet deficient in vitamin A, while Jackson and Riggs [274] were unable to obtain nephritis in the rat by a prolonged high protein diet. Maclean, Smith and Urquhart [275] stressed the necessity of green food to prevent nephritis in the rabbit on a high protein diet. All these factors have a bearing on the liability to infection from septic foci which, even if they are not the primary cause as many believe, are at least a serious com-

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264. Bumpus, H. C., and Meisser, J. A.: Focal Infection and Selective Localization of Streptococci in Pyelonephritis, Arch. Int. Med. **27**:326 (March) 1921; Foci of Infection in Cases of Pyelonephritis, J. A. M. A. **77**:1475 (Nov. 5) 1921.

265. Rosenow, E. C., and Meisser, J. G.: Elective Localization of Bacteria Following Various Methods of Inoculation and the Production of Nephritis by Devitalization and Infection of Teeth in Dogs, J. Lab. & Clin. Med. **7**:707, 1922.

266. Haden, R. L.: The Relation of Chronic Foci of Infection to Kidney Infection, Am. J. M. Sc. **169**:407, 1925.

267. Squier, T. L., and Newburgh, L. H.: Renal Irritation from High Protein Diet, Arch. Int. Med. **28**:1 (July) 1921.

268. Evans, N., and Risley, E. H.: High Protein Ration as Cause of Nephritis, California & West. Med. **23**:437, 1925.

269. Newburgh, L. H., and Clarkson, S.: Renal Injury Caused by Meat Diet, Arch. Int. Med. **32**:850 (Dec.) 1923.

270. Newburgh, L. H.; Marsh, P. L.; Clarkson, S., and Curtis, A. C.: The Dietetic Factor in the Etiology of Chronic Nephritis, J. A. M. A. **85**:1703 (Nov. 28) 1925.

271. Newburgh, L. H.: Etiology of Nephritis, Ann. Clin. Med. **4**:1045, 1926.

272. Peters, J. P., and Bulger, H. A.: The Relation of Albuminuria to the Protein Requirement in Nephritis, Arch. Int. Med. **37**:153 (Feb.) 1926; Nephritis and Nutrition, editorial, J. A. M. A. **86**:1626 (May 22) 1926.

273. Jackson, C. M.: Spontaneous Nephritis and Compensatory Renal Hypertrophy in Albino Rats on Diet Deficient in Vitamin A, Proc. Soc. Exper. Biol. & Med. **22**:410, 1925.

274. Jackson, H., Jr., and Riggs, M. D.: Effect of High Protein Diets on Kidneys of Rats, J. Biol. Chem. **67**:101, 1926.

275. Maclean, H.; Smith, J. F., and Urquhart, A. L.: The Effect of High Protein Diet on Renal Function, Brit. J. Exper. Path. **7**:360, 1927.

plication. A report by Stevens and Dochez [276] demonstrated that rabbits may be rendered allergic to streptococcal filtrates by injections with autolyzed solution from the kidneys of guinea-pigs. What bearing this may have on Forssner's results can only be discovered by further work.

The etiology of urinary calculi will only be briefly touched on. Mayo [277] predicted in 1915 that "it would be found that stones in the kidney and bladder, like pearls in mollusks, were formed by microbic action." In 1922, Rosenow and Meisser [265] were able to fulfil this prediction with staphylococci, and in 1923,[278] with streptococci, according to their reports. Wadsworth [279] reported a case in a patient with nephrolithiasis with an associated streptococcic infection. Cyranka [280] considered that infection with the colon bacillus in the obstructed urine caused precipitation of colloids and crystalloids. After a study of twenty cases, Paul [281] believed osteomyelitis to be the basic cause of nephrolithiasis. Keyser [282] discussed the problem from a chemicomechanical point of view and considered bacteria as the most common causes of the colloidal upset. Bursey [283] found twenty-seven of forty cases associated with focal infection. Rovsing [284] attributed recurrence of kidney calculi after operation to infection, usually wth staphylococci. On the other hand, one sees the effect of a diet deficient in vitamin A in causing experimental calculi, as shown by Osborne and Mendel [285] and confirmed by Fujimaki.[286] I [287] reported a case of a stone in the bladder

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276. Stevens, F. R., and Dochez, A. R.: Cutaneous Reactions with Streptococcus Filtrates in Rabbits Rendered Allergic with Extracts of Guinea-Pig Kidneys, Proc. Soc. Exper. Biol. & Med. **24**:429, 1927.

277. Mayo, C. H.: Infection and Its Relation to General and Local Disease, J. Iowa M. Soc. **15**:546, 1925.

278. Rosenow, E. C., and Meisser, J. G.: The Production of Urinary Calculi by the Devitalization and Infection of Teeth in Dogs with Streptococci from Cases of Nephrolithiasis, Arch. Int. Med. **31**:807 (June) 1923.

279. Wadsworth, A. B.: Nephrolithiasis Purpura Hemorragica and Streptococcus Infection, J. A. M. A. **71**:2052 (Dec. 21) 1918.

280. Cyranka, H.: Bacterium coli und Korallensteinniere, Arch. f. klin. Chir. **116**:567, 1921.

281. Paul, H. E.: Bone Suppuration the Basic Cause of Renal Calculus in Twenty Cases Following War-Wounds, Canad. M. A. J. **12**:638, 1922.

282. Keyser, L. D.: Etiology of Urinary Lithiasis, Arch. Surg. **6**:525 (March) 1923; abstr. J. A. M. A. **80**:1267 (April 28) 1923.

283. Bursey, E. H.: Focal Infection Causes Renal Calculi, Texas State J. Med. **19**:554, 1924.

284. Rovsing, C. M.: Recurrence of Kidney Calculi, Acta. chir. scandinav. **57**:387, 1924; abstr., J. A. M. A. **83**:2056 (Dec. 20) 1924.

285. Osborne, T. B., and Mendel, L. B.: Incidence of Phosphatic Urinary Calculi in Rats Fed on Experimental Rations, J. A. M. A. **69**:32 (July 7) 1917.

286. Fujimaki, Y.: Formation of Urinary and Bile Duct Calculi in Animals Fed on Experimental Rations, editorial J. A. M. A. **88**:1080 (April 2) 1927.

287. Holman, W. L.: Spontaneous Infection in the Guinea Pig, J. M. Research **35**:151, 1916.

of a guinea-pig which died spontaneously with the isolation of *B. lactis aerogenes* from the urine and kidney. I have since seen a large stone in the ureter of a stock guinea-pig which was killed to determine the cause of the swelling.

A considerable number of references suggest the importance of focal infection to the clinical signs of various nephritides, but an attempt will not be made to list them here. Kuczynski [67] quoted Volhard as saying that "about one quarter of all nephritides of known etiology arise alone from a tonsillitis." Hill [288] also gave tonsillitis as the chief cause in childhood. Others believe that the teeth are the primary focus, others, the intestinal tract. Grober and Kaden [289] thought that clinically the so-called "war nephritis" was the end-result of an infection with the streptococcus. Baehr and Lande [290] reported glomerulonephritis after subacute streptococcus endocarditis, and Warwick [291] found that the former could occur without the latter, both usually being caused by *Streptococcus viridans*. The infected kidney may also act as a focus from which bacteria may spread to other organs and tissues, as indicated. The bacteriology of the urine in nephritis and the question of passage of bacteria through uninjured kidneys will not be reviewed, as it is to be found in many of the articles quoted and is treated by Spitzer and Williams.[292]

The good results which have followed the removal or curing of foci of infection on various diseases of the kidney have been frequently reported. I may quote as illustrative the favorable results of Crowe, Watkins and Rothholtz [293] after tonsillectomy in eighteen cases, and of Allison [294] in twelve children. The results in chronic infection are more problematic. Wichert [295] advised removing the tonsils in every case of chronic nephritis.

The general impression to be gained from this review is that many causative factors contribute to the diseases of the kidney and that

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288. Hill, L. W.: Acute Nephritis in Childhood, J. A. M. A. **73**:1747 (Dec. 6) 1919.

289. Grober, J., and Kaden, R.: Zur Atiologie der sog. Kriegsnephritis, München. med. Wchnschr. **68**:99, 1921.

290. Baehr, G., and Lande, H.: Glomerulonephritis as a Complication of Subacute Streptococcus Endocarditis, J. A. M. A. **75**:789 (Sept. 18) 1920.

291. Warwick, M.: Focal Embolic Glomerulonephritis, J. Lab. & Clin. Med. **7**:507, 1922.

292. Spitzer, W. M., and Williams, W. W.: Does Normal Kidney Tissue Permit the Passage of Tubercle Bacilli? J. A. M. A. **88**:1870 (June 11) 1927.

293. Crowe, S. J.; Watkins, S. S., and Rothholtz, A. S.: Relation of Tonsillar and Nasopharyngeal Infections to General Systemic Disorders, Bull. Johns Hopkins Hosp. **28**:1, 1917.

294. Allison, R. S.: Acute Nephritis in Children, Practitioner **114**:222, 1925.

295. Wichert: Die Bedeutung der chronischen Tonsillitis für die chronische Nephritis, München. med. Wchnschr. **73**:1926, 1926.

infection is a most important occurrence in the life cycle of most of the patients. There is no evidence that one type or group of bacteria is the causative agent.

RHEUMATISM

Rheumatism is a most difficult subject to review, chiefly because the term is a clinical one and is particularly ill defined. In outspoken examples of acute rheumatic fever as a systemic disease, with a more or less complete upset of the capillary circulatory mechanism, and as manifested in the perivascular zones of reaction and showing its effects in regions usually having a relatively poor vascular supply, such as the joints and endocardium or in tissues in which numerous factors affect the finer circulation, as in the heart muscle and skin, there is comparatively little difficulty in diagnosing the disease. But a "history of rheumatism" includes every grade of minor disturbance from the "growing pains" of children and the various manifestations of myositis, fibrositis and arthritis to the severe signs of involvement of individual organs in pancarditis, chorea and erythema nodosum and other skin diseases, if these may be included (Ingerman and Wilson [296]).

I believe that the fundamental basis of all these rheumatic manifestations is a condition of hypersensitiveness to numerous exciting causes. To determine what are the causes of this hypersensitive condition is a more difficult matter. The capillaries are the site of the cellular exchange and on them depends the healthy metabolism of the tissues. Faulty function is the chief cause of pain and may result in local damage, making the capillaries less adaptable to future healthy reaction. The many factors affecting function of the capillaries must be thought of in every case. The effect of cold on the skin, with the local and reflex results, the taking of unaccustomed exercise and the exposure to cold during the readjustment of the circulation, reflexes from conditions of intestinal irritation, the effect of deficient or faulty food, anaphylactic shock, often subclinical, the fatigue of continual overuse of any organ or tissue and many more factors complicated by toxemia or infection from infected foci must be carefully considered before one can hope to find the actual fundamental trouble. It is to be expected that large groups of persons respond to common influences which give rise to the clinical entity of acute rheumatism, but the multiplicity of underlying factors accounts for the more numerous varieties of other manifestations.

The earnest attempts to discover a specific causative factor for the main disease, as well as the other manifestations, have been beset with many difficulties. This is largely due to the fact that in man, under the variety of associated or preceding conditions cited, a great many

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296. Ingerman, E., and Wilson, M. G.: Rheumatism: Its Manifestations in Childhood Today, J. A. M. A. **82**:759 (March 8) 1924.

different bacteria will bring about similar results. Arthritis, endocarditis, myocarditis, myositis and other diseases may be caused by streptococci, pneumococci, staphylococci, gonococci and many other bacteria, and the response to these infections depends on the condition of the body at the particular time of the chance infection. In animal experiments, rigid criteria are lacking for identifying the disease experimentally produced with that in the human patient. The Aschoff bodies, which are considered by many as the pathognomonic pathologic sign, are often absent in patients with a definite history of acute rheumatic fever, and are present when such a history cannot be obtained. Geipel [297] and many others have shown that the percentage of positive results is low. It would appear, however, that it is a characteristic reaction of the tissues under the general conditions associated with the disease. In animals, when one depends almost entirely on relatively massive doses of bacteria, this type of response is not often exactly reproduced. Clawson [298] discussed this problem, and it may be pointed out that, with the more careful study of late years, the frequency of finding such a type of reaction and the evidence of its relationship to rheumatic infection has increased.

I will not attempt to review the contributions bearing on the bacterial etiology of this disease. This has been done by Bracht and Wächter,[299] Poynton and Paine,[300] Coombs,[301] Clawson [298] and Birkhaug.[39] Streptococci of various kinds have been the micro-organisms most seriously considered, and the work of Rosenow [302] on the rheumatic diseases did a great deal to attract attention to the importance of foci of infection. The medical profession, however, has not been convinced that a specific germ has been discovered, and this is due in a great measure to the lack of agreement by the investigators as to the type of streptococcus believed to be the causative agent. Clawson [298] concluded from his studies and the reports of others that "the group cannot be considered a specific one, but

297. Geipel, P.: Ueber Myokarditis und Veränderung der quergestreiften Muskeln bei Rheumatismus, München. med. Wchnschr. **56**:2469, 1909.

298. Clawson, B. J.: Studies on the Etiology of Acute Rheumatic Fever, J. Infect. Dis. **36**:444, 1925.

299. Bracht, E., and Wächter: Beitrag zur Etiologie und pathologische Anatomie der Myocarditis rheumatica, Deutsches Arch. f. klin. Med. **96**:493, 1909.

300. Poyton, F. J., and Paine, A.: Researches on Rheumatism, London, J. & A. Churchill, 1913.

301. Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood & Co., 1924.

302. Rosenow, E. C.: Etiology of Articular and Muscular Rheumatism, J. A. M. A. **60**:1223 (April 19) 1913; The Etiology of Acute Rheumatism, Articular and Muscular, J. Infect. Dis. **14**:61, 1914. Rosenow, E. C., and Ashby, W.: Focal Infection and Elective Localization in the Etiology of Myositis, Arch. Int. Med. **28**:274 (Sept.) 1921. Rosenow, E. C.: Experimental Observations on Etiology of Chorea, Am. J. Dis. Child. **26**:223 (Sept.) 1923.

that it represents a heterogeneous group, generally green producers with moderately low virulence." After almost thirty years, Singer [303] still believed in the streptococcic etiology; he believed further that articular rheumatism, endocarditis lenta and viridans sepsis are all stages in a long procession in which, for the particular localization and the clinical form, constitutional differences play a rôle. Small [304] was convinced on comparatively meager grounds that his *Streptococcus cardioarthritidis* is the specific cause.[305]

Birkhaug [39] added materially to the knowledge of rheumatic fever. He was able to isolate from the blood, tonsils, feces and abscesses of patients with rheumatic fever sixty-eight strains of a streptococcus that did not form methemoglobin but which fermented inulin and which he considered the etiologic agent. This nonhemolytic character may be important, but when one realizes the work being done on the alteration of hemolytic and green producing characters in streptococci, it should not be stressed unless it is most carefully controlled. Clawson [298] found that his nonhemolytic strains often became green producing on transfer, and I [12] have found the same. Brown [306] and many others considered it a fixed character, and for certain strains it may well be. Birkhaug did not stress this particular point of fixity of character. I found that his agglutination tests did not show a greater group tendency than they have shown in many earlier attempts to classify streptococci by this means. The homologous strain showed specific agglutination, but from the twenty-six strains listed in Birkhaug's table only twelve agglutinated above the fourth tube while seven gave apparently negative results and two agglutinated with antiviridans serum in the fourth tube. The most important part of his work, however, concerned production of specific toxin, and in this regard it is unfortunate that he did not stipulate when the whole filtrate and when purified toxin was used in his experiments. In the earlier part of this review, I have mentioned the possible significance of general hypersensitiveness in this disease.

The praiseworthy experiment on himself clearly demonstrated the great importance of such toxic products of streptococcic origin (he used the purified toxin) in bringing on an attack of typical acute polyarthritis. But without intending to underestimate the dominating significance of

303. Singer, G.: Die akute rheumatische Polyarthritis als Streptokokkenkränkheit, Med. Klin. **21**:1530, 1925.

304. Small, J. C.: The Bacterium Causing Rheumatic Fever and a Preliminary Account of the Therapeutic Action of Its Specific Antiserum, Am. J. M. Sc. **173**:101, 1927.

305. Has the Bacterium of Rheumatic Fever Been Discovered? editorial, J. A. M. A. **88**:326 (Jan. 29) 1927; The Organism of Rheumatic Fever, ibid. **88**:405 (Feb. 5) 1927.

306. Brown, J. H.: The Use of Blood Agar for the Study of Streptococci, Monograph of the Rockefeller Institute for Medical Research, no. 9, 1919.

this in many cases, I must point out that many other conditions have similar effects, such as exposure to cold, constipation, fatigue and, as Loeffler [307] has recently reported, too long an exposure to a sun bath. I do not wish to leave the impression of being unduly critical of this investigation, because I believe that in it is the foundation for a most important approach to the subject of rheumatism.

The chief difficulty in trying to determine the clinical evidence of a relationship between focal infections and rheumatism has been the variability in the nature of the attacks. In some cases the polyarthritis is the symptom stressed, in some, chorea, subcutaneous nodules, or various indications of involvement of the heart. Peabody,[308] White [309] and Poynton [310] reported heart block as the primary significant symptom in certain cases. Acute infections in the upper respiratory tract have been frequently reported as preceding rheumatism. It is not always clear whether these are part of a systemic disease or the forerunner of it. Groedel [311] well expressed the views of many when he considered that the angina was a local condition permitting the entrance of the coccus and that acute rheumatism only followed when there was a disposition to the disease; otherwise, diseases of the kidneys, lymph glands, or vague rheumatic pains in the bones and joints or, indeed, no distant reaction resulted. Infections in and about the tonsils are the commonest associations noted. In the report of the Ministry of Health, Newman [312] stated that tonsillar sepsis may be an important etiologic factor in acute and subacute rheumatism and that in forms of fibrosis and chronic disease of the joints, an impression was gained that dental sepsis may be a factor. However, since roentgenologic records were not included, the evidence is perhaps less than might have appeared. The results of tonsillectomy in preventing recurrences are generally favorable in most of the reports published. In twenty-five patients with rheumatism, Crowe, Watkins and Rothholtz [293] found only four recurrences after the operation. Nordlund [313] also reported favorable results. Lambert [314] gave credit

307. Loeffler, G.: Akute Gelenkentzündung nach Sonnenbrand, Med. Klin. **22**:1452, 1926.

308. Peabody, F. W.: Heart-Block Associated with Infectious Diseases, Arch. Int. Med. **5**:252 (March) 1910.

309. White, P. D.: Acute Heart Block Occurring as the First Sign of Rheumatic Fever, Am. J. M. Sc. **152**:589, 1916.

310. Poynton, F. J.: Acute Rheumatism, Arch. Dis. Child. **2**:62, 1927.

311. Groedel: Ueber Acuten Gelenkrheumatismus im Anschluss an Angina, Deutsche med. Wchnschr. **22**:259, 1896.

312. Newman, G.: Ministry of Health: The Incidence of Rheumatic Diseases, Reports on Public Health and Medical Subjects, no 23, London, 1924.

313. Nordlund, H.: Tonsillectomy and Rheumatism, Hygiea **81**:497, 1919; abstr., J. A. M. A. **73**:568 (Aug. 16) 1919.

314. Lambert, A.: The Incidence of Acute Rheumatic Fever at Bellevue Hospital, J. A. M. A. **74**:993 (April 10) 1920.

for the lessening incidence of acute rheumatic fever to both dental hygiene and tonsillectomy. St. Lawrence [315] did not report recurrences after tonsillectomy in 85 per cent of patients with acute rheumatc fever, in 50 per cent of patients with chorea and in 77 per cent of patients with myositis and pains in the bones or joints. Hunt [316] found that tonsillectomy had little, if any, effect on recurrences. Mackie [317] presented strong evidence of the importance of tonsillar infection in rheumatism and reported that 93 per cent of patients in whom the first attack occurs under the tenth year have recurrences. He favored tonsillectomy as reducing the recurrences only if the tonsils are actually infected. Robey and Freedman [318] considered complete enucleation of the tonsils to be the best preventive of rheumatic fever and, therefore, of rheumatic heart disease.

JOINTS

A number of considerations make it advisable to review disease of the joints apart from rheumatism, although it is so frequently a part of that condition. The first is that arthritis may be only an incident in rheumatism and that the changes in the joint in rheumatism are believed to differ from all other infections in affecting especially the periarticular tissues and in not being destructive (MacCallum [319]). It is also well known that almost every infective bacterium may attack the joints and that most of these infections have effects that are different from that which is usually found in rheumatism. The circulation is at the basis of all these infections, and in rheumatism the reaction is different, probably being the result of the type of bacteria usually concerned and the hypersensitive condition of the patient. Certainly the reactions of the joints in rheumatism are largely reflex. Joints are liable to become infected after intravenous injection of many kinds of bacteria, and the periarticular tissues are nearly always first attacked, whether this progress depends on the virulence or on the pathogenicity of the bacterium. McMeans [320] published a useful discussion on experimental

315. St. Lawrence, W.: Effect of Tonsillectomy on the Recurrence of Acute Rheumatic Fever and Chorea, J. A. M. A. **75**:1035 (Oct. 16) 1920.

316. Hunt, G. H.: Results of Tonsillectomy in Acute Rheumatism in Children, Guy's Hosp. Rep. **73**:383, 1923; abstr., J. A. M. A. **82**:231 (Jan. 19) 1924.

317. Mackie, T. T.: Rheumatic Fever: An Analytical Study of Three Hundred and Ninety-Three Cases of Rheumatic Fever and Eighty-Nine Cases of Chorea, Am. J. M. Sc. **172**:199, 1926.

318. Robey, W. H., and Freedman, L. M.: The Effects of Tonsillectomy on the Acute Attack and Recurrence of Rheumatic Fever, Boston M. & S. J. **196**:595, 1927.

319. MacCallum, W. G.: Rheumatism, J. A. M. A. **84**:1545 (May 23) 1925.

320. McMeans, J. W.: Experimental Bacteremia, Arch. Int. Med. **22**:617 (Nov.) 1918.

bacteremia and considered many of the factors involved. Wilensky [321] reported on the mechanism of acute bacterial infection of a joint, and Johnson [322] carefully described the blood supply of the bones. The differences in blood supply at different ages and the alteration produced by previous injury, whether it was of mechanical or bacterial origin, will account for most of the infections coming from a focus elsewhere.

The early work of Koch [323] on infection in young animals and his attempt, with that of many others, to prove the bacterial nature of scurvy should make one consider more carefully when infection is of prime importance and when it is not. The effect of cold in determining infection of the joints has been fully realized, and the benefit derived from warmth is well illustrated by the studies of Simmonds and Moore [324] and Pemberton.[325] The importance of diet suggested in Koch's work has been particularly stressed in recent years because of its effect on the permeability of capillaries. A high carbohydrate diet has also been shown to be frequently detrimental in patients with arthritis, particularly by Pemberton [326] and Fletcher.[327] Further studies by Pemberton [328] have included the examination of other factors affecting the circulation and the nutritional condition of the joints. A number of reports have appeared which stress the occurrence of anaphylactic phenomena, which, as is well known, have a marked effect on the endothelia of the capillaries. The nonspecific protein therapy apparently

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321. Wilensky, A. O.: The Mechanism of Acute Bacterial Infection of a Joint, Arch. Surg. **13**:895 (Dec.) 1926.

322. Johnson, R. W.: Blood Supply of Diaphysis, J. Bone & Joint Surg. **9**: 153, 1927.

323. Koch, J.: Untersuchungen über die Lokalisation der Bakterien, das Verhalten des Knochenmarks und die Veränderungen der Knochen, insbesondere der Epiphysen bei Infektionskrankheiten. Mit Bemerkungen zur Theorie der Rachitis, Ztschr. f. Hyg. u. Infectionskrankh. **69**:436, 1911; Lokalisation der Bakterien, die Veränderungen der Knochenmarks und der Knochen bei Infektionskrankheiten in ersten Wachstums Alter, Berl. klin. Wchnschr. **6**:289, 1914.

324. Simmonds, W. E., and Moore, J. J.: The Effect of Heat and Continuous Incandescent Electric Light in Experimental Arthritis, Arch. Int. Med. **19**:153 (Jan.) 1917.

325. Pemberton, R., and Crouter, C. Y.: The Response to the Therapeutic Application of External Heat, J. A. M. A. **80**:289 (Feb. 3) 1923. Pemberton, R.: Effects of External Heat on Human Body, Am. J. M. Sc. **169**:485, 1925; Physiologic Effect of External Heat on Human Body, Ann. Clin. Med. **5**:763, 1927.

326. Pemberton, R.: Restricted Carbohydrate Diet in Arthritis, Arch. Int. Med. **25**:351 (April) 1920; The Use of Diet in the Treatment of Chronic Arthritis, Am. J. M. Sc. **161**:517, 1921.

327. Fletcher, A. A.: Dietetic Treatment of Chronic Arthritis and its Relationships to Sugar Tolerance, Arch. Int. Med. **30**:106 (July) 1922.

328. Pemberton, R.; Cajori, F. A., and Crouter, C. Y.: The Physiologic Effect of Massage, J. A. M. A. **83**:1761 (Nov. 29) 1924.

owes its good effects to some such action, although the absence of eosinophilia was considered by Cowie and Calhoun [329] to rule this out, and they explained the favorable results on the basis of other changes in the blood cells. The work of Boots and Swift [330] suggested that the local irritation of foreign serum in an allergic tissue accounted for the arthritis of serum sickness. Turnbull [331] believed that in the absence of infected foci food hypersensitiveness may be responsible for certain cases. Cecil and Archer [332] reported on cases in which arthritis occurred during the menopause, and as is well known, this is a period of marked circulatory disturbance.

I think it will be evident that many factors play a part in these conditions of the joints, and infection combined with certain of these factors may often change a mild arthritis into a serious disease. The evidence pointing to the significance of focal infection in the etiology has been incorporated in reports appearing under other headings. A few additional ones may be cited. In the study of 104 patients with arthritis, Richards [333] incriminated the following foci as harboring *Streptococcus viridans:* the teeth, in 50; the tonsils, in 40; the accessory nasal sinuses, in 11; the prostate in 2, and pyelitis and salpingitis, 1 each. Mutch [334] reported 200 cases of chronic arthritis, with active sepsis in the throat in 34 per cent, dental sepsis in 52 per cent and "infective" streptococci from the feces in 84 per cent. Miller and Smith [101] have criticized Mutch's report, in that the term "infective" was not defined and the results in normal cases not reported. Kinsella [335] emphasized the importance of circulatory changes with resultant nutritional changes and the need of exhaustive examination for infected foci. Moench [336] called attention to chronic endocervicitis as important in chronic arthritis. Pemberton, Cajori and

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329. Cowie, D. M., and Calhoun, H.: Nonspecific Therapy in Arthritis and Infections, Arch. Int. Med. **23**:69 (Jan.) 1919.

330. Boots, R. H., and Swift, H. F.: The Arthritis of Serum Sickness, J. A. M. A. **80**:12 (Jan. 6) 1923.

331. Turnbull, J. A.: The Relation of Anaphylactic Disturbances to Arthritis, J. A. M. A. **82**:1757 (May 31) 1924.

332. Cecil, R. L,. and Archer, B. H.: Arthritis of the Menopause, J. A. M. A. **84**:75 (Jan. 10) 1925.

333. Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bacteriol. **5**:511, 1920.

334. Mutch, N.: Alimentary Infections in Chronic Arthritis, Lancet **2**:1266, 1921.

335. Kinsella, R. A.: Chronic Infectious Arthritis, J. A. M. A. **80**:671 (March 10) 1923.

336. Moench, L. M.: The Relationship of Chronic Endocervicitis to Focal Infection with Special Reference to Chronic Arthritis, J. Lab. & Clin. Med. **9**:289, 1924.

Crouter [337] showed that 60 per cent of arthritic patients presented a lowered sugar tolerance and that this returned to normal after recovery but that it did so most abruptly after the removal of the causative focal infections. Pemberton [338] previously stressed the point that an arthritis from focal infection or exposure may have so dislocated the function of the joint that removal of the cause is no longer adequate for recovery. He and his associates are adherents to the belief that closed capillary beds are at the root of this disease. Cecil and Archer [339] found that in about two thirds of the cases of chronic arthritis the condition was of the proliferative type and was associated with foci of infection about the teeth and tonsils, the former more often in older persons and the latter in young people.

HEART

The involvement of the heart—the myocardium, endocardium or pericardium—is so frequent in infections of the focal type that careful attention must be given to it. The most important consideration in the anatomy is the capillary circulation, because it is here that stoppage of bacteria in the blood must almost exclusively occur. Bayne-Jones [340] clearly demonstrated blood vessels in the valves of the human heart. He found the vessels in the atrioventricular valves ramified chiefly along the line of closure of these valves, where arteries, veins and an anastomosing capillary bed were seen. Other distributions of vessels were given, and on these he based an anatomic conception of the embolic origin of endocarditis. Gross [341] analyzed the clinical aspects of the general blood supply of the heart. In studying the capillary bed particularly, Wearn [342] found about one capillary to each muscle fiber. He noted that most of these capillaries were closed when the heart was dilated, and that under these conditions the return of blood to the chambers of the heart is largely by the thebesian vessels. He found an irregular and less abundant supply of capillaries in the auricles. The valves and the walls

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337. Pemberton, R.; Cajori, F. A., and Crouter, C. V.: Influence of Focal Infection and the Pathology of Arthritis, J. A. M. A. **85**:1793 (Dec. 5) 1925; ibid. **87**:2148 (Dec. 25) 1926.

338. Pemberton, R.: The Nature of Arthritis and Rheumatoid Conditions, J. A. M. A. **75**:1759 (Dec. 25) 1920; Further Observations on Arthritis and Rheumatoid Conditions, Am. J. M. Sc. **166**:833, 1923.

339. Cecil, R. L., and Archer, B. H.: Classification and Treatment of Chronic Arthritis, J. A. M. A. **87**:741 (Sept. 4) 1926; Chronic Infectious Arthritis, Am. J. M. Sc. **173**:258, 1927.

340. Bayne-Jones, S.: The Blood Vessels of the Heart Valves, Am. J. Anat. **21**:449, 1917.

341. Gross, L.: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921.

342. Wearn, J. J.: Extent of Capillary Bed and Rôle of Thebesian Vessels in Coronary Circulation, Proc. Soc. Exper. Biol. & Med. **23**:707, 1926.

of the aorta also showed vessels by his method of injection, and on one occasion an anastomosis between a vessel in a papillary muscle and a vessel in a valve was seen.

When one considers these facts and the well known variability and diminution in the blood supply, particularly of the valves in childhood, together with the recognition that the initial attack or infection usually takes place in the early years of life, one has, I believe, a reasonable explanation for the incidence and sites of infection in most cases of disease of the heart. The numerous conditions liable to affect the capillary endothelia, many of which have already been cited, must here be considered and the rapid production of new capillaries, probably much less resistant, about an area of infection should be looked on as helping to explain the course and outcome of recurrent infections. Lewis and Harmer [343] showed that the minute vessels of the skin break under relatively low strain in patients with subacute infective endocarditis. Walker [344] quoted Mackenzie as believing that the myocardial degeneration of old age results from progressive obliteration of capillaries. The continual motion, accentuated at certain points, such as occurs about the edges of closure of the valves, interferes with healing and results in types of reaction not so often found in other regions.

The serious result of the rheumatic infection is undoubtedly the damage done to the heart. As Coombs [301] has emphasized, it is usually a pancarditis but the variability in the sites of maximum damage is great. The finding of Aschoff nodules in greater abundance in certain areas, as shown by MacCallum [345] and many others, points to this type of reaction as being characteristic for rheumatism. These areas and many more in various stages of development or healing are, without question, sites of lowered resistance to subsequent infections.

Experimental infection of the heart is comparatively easy to produce in animals, but sufficient attention has not been paid to the age of the animals nor to the distribution of vessels in the different species. The presence of spontaneous lesions as indicating susceptibility has also not been sufficiently stressed. As an example of the frequency of such lesions, Miller [346] found that 60 per cent of his thirty-four healthy adult rabbits showed an interstitial myocarditis without any evidence of bacterial infection. It is obvious that an intravenous injection into such a

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343. Lewis, T., and Harmer, I. M.: Rupture of Minute Vessels in Skin, Heart **13**:337, 1926.

344. Walker, H. M.: Disorders of Capillary Vessels as Factor in Disease, Glasgow M. J. **23**:286, 1926; ibid. **24**:240, 1926.

345. MacCallum, W. G.: Rheumatic Lesions of the Left Auricle of the Heart, Bull. Johns Hopkins Hosp. **35**:329, 1924.

346. Miller, C. P.: Attempts to Transmit Rheumatic Fever to Rabbits and Guinea-Pigs, J. Exper. Med. **40**:525, 1924

group of animals would give a high incidence of cardiac involvement. It will be impossible to review the numerous reports on experimental cardiac disease. The work of Rosenow is well known and will be considered later. Detweiler and Robinson [347] found that *Streptococcus viridans,* as isolated from chronic infectious endocarditis, is of low virulence and produced endocarditis in rabbits as did strains from the mouth of normal persons. There are many similar reports. Mair [348] found a high incidence of fatal infective endocarditis after injection of pneumococcus in rabbits which had previously been treated with pneumococcus filtrate. Kinsella and Garcia [349] stated that it is easy to produce endocarditis in dogs with a strain of streptococcus from a patient with rheumatic fever, but he was unable to do so with strains from patients with subacute streptococcus endocarditis. From other experiments, they suggested that the latter cultures are in effect "sensitized" or agglutinated cultures. From a careful study of patients with acute rheumatic and subacute bacterial endocarditis and from experiments on rabbits, Clawson and Bell [350] concluded that "the streptococci, generally the viridans strains, seem to be responsible for both rheumatic and subacute bacterial endocarditis." The various lesions found were looked on as only stages in the cycle of the reaction to the causative agent. Evidence that cardiac defects are at the basis of many infections is to be found in such reports as those of Abbott,[351] Clawson, Bell and Hartzell [352] and the early experiment of Blum.[4]

Endocarditis may be caused by a great variety of bacteria—*M. zymogenes,*[353] the pneumococcus, *B. influenzae,* the gonococcus, *Staphylococcus aureus, Streptococcus hemolyticus* and many more. Karsner [354] found acute valvulitis as a complication in a series of soldiers who had been wounded. Myocarditis is also a complication of a great

347. Detweiler, H. K., and Robinson, W. L.: Experimental Endocarditis, J. A. M. A. **67**:1653 (Dec. 2) 1916.

348. Mair, W.: Pneumococcal Endocarditis in Rabbits, J. Path. & Bact. **26**: 426, 1923.

349. Kinsella, R. A., and Garcia, O.: A Clinical Experiment in Subacute Streptococcus Endocarditis, Proc. Soc. Exper. Biol. & Med. **23**:136, 1925.

350. Clawson, B. J., and Bell, E. T.: A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **37**:66 (Jan.) 1926.

351. Abbott, M. E.: On the Incidence of Bacterial Inflammatory Processes in Cardiovascular Defects and on Malformed Semilunar Cusps, Ann. Clin. Med. **4**:189, 1925.

352. Clawson, B. J.; Bell, E. T., and Hartzell, T. B.: Valvular Diseases of the Heart, Am. J. Path. **2**:193, 1926.

353. MacCallum, W. G., and Hastings, T. W.: A Case of Acute Endocarditis Caused by Micrococcus Zymogenes (nov. spec.) with a Description of the Microorganism, J. Exper. Med. **4**:521, 1899.

354. Karsner, H. T.: Acute Endocarditis Following War Wounds, Arch. Int. Med. **22**:296 (Sept.) 1918.

many diseases. Nevertheless, the frequency of nonhemolytic streptococci, usually of the viridans type, associated with at least certain stages of these conditions, has drawn the major amount of attention to this group. As has been repeatedly stressed, these streptococci are highly invasive; they occur with great regularity in the various foci often suspected in such cases; they are able to locate in the tissues of animals and bring about comparable lesions, and therefore they are often held responsible. Much of the evidence advanced under the descriptions of rheumatism and arthritis as favoring or disfavoring the principle of focal infection as applied here could be transferred. The heart in bacterial endocarditis, however, becomes a focus of infection in itself and as such gives rise to easily demonstrable distant infection, frequently embolic, in the kidneys, spleen, brain, skin and other sites. The evidence for this is too well recognized to need support here.

The beneficial results of removing what may have been the original foci after the establishment of the focus in the heart are, of course, much less effective, and the same is often true in the other conditions already discussed. Harrison [355] advocated the removal of the tonsils during an acute attack of endocarditis. Floyd [356] found the teeth involved in three of four patients with chorea and the tonsils in one. In patients with mitral and aortic disease, Starling [357] found an incidence of tonsillar infection of 81 per cent in patients under thirty and of 61 per cent in those over thirty. Antonius and Czepa [86] found that twenty-nine of his forty patients with endocarditis showed periapical infection of the teeth.

OTHER DISEASES AND FOCAL INFECTIONS

I have not undertaken to review the work done on chorea, encephalitis, poliomyelitis and other diseases of the nervous system, nor those of the skin, eye, thyroid, prostate and ovary.

I recognize the infections of the paranasal sinuses as of importance in focal infection, but space prevents me from giving them adequate consideration. The same principles of infection hold good for these sinuses. Because of their structure, I do not feel that they are as frequent sources of infection as those I have discussed; in this I agree with Canfield,[48] although Kolmer [37] gave them second place and Byfield,[358] Arbuckle,[359]

355. Harrison, W. G.: Tonsillectomy During Acute Endocarditis, South. M. J. **8**:59, 1915; abstr., J. A. M. A. **64**:543 (Feb. 6) 1915.

356. Floyd, C.: A Study of Streptococci Obtained from the Mouth in Cases of Chorea, J. M. Research **41**:467, 1920.

357. Starling, H. S.: Tonsillar and Rheumatic Infections, Guy's Hosp. Rep. **73**:388, 1923; Miscellany, J. A. M. A. **82**:57 (Jan. 5) 1924.

358. Byfield, A. H.: Systemic Manifestations of Chronic Nasal Sinus Infection in Childhood, J. A. M. A. **71**:511 (Aug. 17) 1918.

359. Arbuckle, M. F.: Systemic Manifestations of Suppurative Disease in Paranasal Sinuses, J. A. M. A. **81**:741 (Sept. 1) 1923.

who emphasized their development at an early age, Clausen,[360] who considered them important in certain cases, and Jeans [361] have all called attention to probable infection from them. There is much evidence in favor of focal infection playing a part in skin infections. Ravitch [362] discussed this, and it has many important bearings on the problem of focal infections. Osteomyelitis is today generally recognized as depending almost exclusively on staphylococcus lesions in the skin. The eye also deserves more attention than I can give it. The relationship between infections about the teeth and various forms of disease of the eyes has been stressed by many investigators, and Irons and Brown [363] showed the excellent results obtained by removal or treatment of the suspected focus of infection. The thyroid has also been thought to be included in the organs affected by focal infection. The work of Olesen and Taylor [364] on more than 15,000 children suggested a deleterious influence on enlargement of the thyroid by defective teeth and diseased tonsils in cases in which deficiency of iodine was not involved. A number of references have already been made to prostatic infections, both as primary and secondary foci. Walther [365] treated this subject in a short article and included a list of disease conditions thought to be caused by chronic prostatitis.

SOME FACTORS DETERMINING INFECTION

In the foregoing review, certain facts and fancies connected with the principle of focal infection have been brought together. I have stressed certain observations in which I have felt that they had not been sufficiently appreciated by investigators in the past. There are, however, certain basic principles of infection which should be more fully discussed, since they apply closely to focal infection.

It is generally recognized that a great variety of bacteria are present in the oral cavity and in the intestinal tract, and that, although the flora changes under many conditions, certain types remain relatively constant and these consist of those bacteria which have colonized. In a series of

360. Clausen, S. W.: Nephritis in Children, Atlantic M. J. **29**:201, 1926.

361. Jeans, P. C.: Paranasal Sinusitis in Infants and in Young Children, Am. J. Dis. Child. **32**:40 (July) 1926.

362. Ravitch, M. L.: Focal Infection in Relation to Certain Dermatoses, J. A. M. A. **67**:430 (Aug. 5) 1916; Ravitch, M. L., and Steinberg, S. A.: Relationship of Focal Infections to Certain Dermatoses, ibid. **71**:127 (Oct. 19) 1918.

363. Irons, E. E., and Brown, E. V. L.: The Etiology of Iritis, J. A. M. A. **81**:1770 (Nov. 24) 1923.

364. Olesen, R., and Taylor, N. E.: The Relationship of Endemic Goiter to Certain Potential Foci of Infection, Pub. Health Rep. **41**:557, 1926; Further Studies on the Relationship of Endemic Goiter to Certain Potential Foci of Infection, ibid. **42**:606, 1927.

365. Walther, H. W. E.: Prostatitis; Its Rôle in Focal Infection, New Orleans M. & S. J. **78**:493, 1926.

articles, Bloomfield [366] discussed the various factors involved in these conditions and his demonstration of the practical impossibility of sterilizing the mucous membrane was of particular interest. He believed that this was due to the fact that the bacteria were growing not only on the mucous membrane but in the superficial layers, in crevices between the epithelia and in the orifices of the small mucous glands. Are such niduses of growth to be considered as foci of infection? This is certainly the "normal" condition found, and I should think that such an interpretation would be too broad. Infected foci should include only those in which a demonstrable zone of reaction is present.

COMMON COLDS

The number of factors determining the incidence of "common colds" are of great importance, because it is frequently during these "colds" that the various foci become established and at this time probably many of the actual foci of infection become systemic. This is a complicated subject. Mudd, Grant and Goldman [367] have given a comprehensive analysis of many of the determining factors. They particularly stressed the importance of chilling, and they considered that the mechanism involved was a reflex one. They further demonstrated that vasoconstriction and ischemia of the mucous membrane resulted from such chilling. In their discussion was included the combined effect, emphasized by Hill and Muecke,[368] of overheated rooms causing congestion and hyperactivity to the point of fatigue, and which resulted in ischemia when followed by exposure to cold. It is a question, therefore, involving the consideration of the factors influencing the circulatory mechanism.

366. Bloomfield, A. L.: The Fate of Bacteria Introduced Into the Upper Air Passages, Am. Rev. Tuberc. **3**:553, 1919; The Localization of Bacteria in the Upper Air Passages; Its Bearing on Infection, Bull. Johns Hopkins Hosp. **32**:290, 1921; The Mechanism of the Carrier State, with Special Reference to Carriers of Friedländer's Bacillus, ibid. **32**:10, 1921; Adaptation of Bacteria to Growth on Human Mucous Membranes with Special Reference to the Throat Flora of Infants, ibid. **33**:61, 1922; The Dissemination of Bacteria in the Upper Air Passages: The Circulation of Bacteria in the Mouth, ibid. **33**:145, 1922; The Dissemination of Bacteria in the Upper Air Passages; The Relation of Bacteria to the Mucous Membranes, ibid. **33**:252, 1922; The Effect of Antiseptics on the Bacterial Flora of the Upper Air Passages, ibid. **34**:65, 1923.

367. Mudd, S., and Grant, S. B.: Reactions to Chilling of the Body Surface. Experimental Study of a Possible Mechanism for the Excitation of Infections of the Pharynx and Tonsils, J. M. Research **40**:53, 1919. Mudd, S.; Grant, S. B., and Goldman, A.: The Etiology of Acute Inflammations of the Nose, Pharynx and Tonsils, J. Lab. & Clin. Med. **6**:322, 1921; The Etiology of Acute Inflammations of the Nose, Pharynx and Tonsils, Ann. Otol. Rhin. & Laryng. **30**:1, 1921; Reaction of Nasal Cavity and Postnasal Space to Chilling of the Body Surface, J. Exper. Med. **34**:11, 1921.

368. Hill, L., and Muecke, F. F.: "Colds in the Head" and the Influence of Warm Confined Atmospheres on the Mucous Membrane of the Nose and Throat, Lancet **1**:1291, 1913.

A capillary system capable of adapting itself to such emergencies will undoubtedly usually prevent such infections.

The bacteria found in these cases [369] of "colds" are so variable that no one type can be held responsible for the effects that follow the complicating infections. The final result of such conditions is often the establishment of infected foci in the oral cavity, and the bacteria that are found under these circumstances are largely streptococci and pneumococci.

I do not wish to give the impression that I consider cold and heat the only factors involved in these disturbances of the capillaries, and certainly the foregoing authors did not believe this nor that such effects are confined to the respiratory tract. Sayers and Davenport [370] reviewed the literature on the effects of temperature and humidity on the general functions of man, and a great deal of work has been done indicating their importance. The changes brought about by many of these factors in the physical and chemical composition of the blood must also be considered, as they alter the flow of blood in the capillaries. Barbour and Hamilton [371] reported an interesting series of results on the topic of heat regulation and water exchange, and Green and Rowntree [372] showed the dangers of excess water intake. Macleod and Taylor [373] stressed the importance of the penetration of the tissues by local heat and cold but they did not underestimate the reflex effects so well established; Septelici,[374] also, reported on the changes brought about by cold.

HEAT AND COLD

The effects of heat and cold on experimental infection has been known since the work of Pasteur on anthrax. When attempts are made to raise the virulence of pneumococci by experiments on animals a common method is to expose to cold white mice in which injections of pneumococci have been made. In his experiments on arthritis,

369. Shibley, G. S.; Hanger, F. M., and Dochez, A. R.: Observations of the Normal Bacterial Flora of Nose and Throat with Variations Occurring During Colds, J. Exper. Med. **43**:415, 1926.

370. Sayers, R. R., and Davenport, S. J.: Review of Literature on the Physiological Effects of Abnormal Temperatures and Humidities, Pub. Health Rep. **42**:933, 1917.

371. Barbour, H. G., and Hamilton, W. F.: Heat Regulation and Water Exchange, Am. J. Physiol. **73**:315, 1925.

372. Green, C. H., and Rowntree, L. G.: Effect of Excessive Amounts of Water, Am. J. Physiol. **80**:209, 1927.

373. Macleod, J. J. R., and Taylor, R. B.: Effects of Hot and Cold Applications to the Surface of the Body, on the Temperature of the Muscles, Liver, Kidneys and Brain, Lancet **2**:70, 1921.

374. Septelici, L.: Modification de l'etat physico-chemique du sang sous l'action locale du froid, Compt. rend. Soc. de biol. **94**:716, 1926; Réaction morphologique (specto-réaction) sous l'action locale du froid dans differents cas pathologiques, ibid. **94**:893, 1926.

Rosenow [302] reported that if the animals were exposed to cold more of them showed infections of the joints. McDowell [375] studied the effects of varying temperature and humidities on the resistance of rats to intraperitoneal injections of pneumococcus. Müller [376] showed that animals kept at a temperature of from 35 to 37 C. were more resistant to infection with *B. anthracis* than those kept at normal temperatures and stressed the importance of the temperature of the skin in this changed susceptibility. Schamberg and Rule [377] were able to cure rabbits of experimental primary syphilis by hot baths. The most logical explanations of such results are the effects on the capillary circulation and the prevention of further colonization. However, there are many other conditions that have deleterious effects on the delicate endothelium of capillaries. I have briefly referred to constipation. Fatigue from overwork of any tissue or organ, nervous conditions with a hyperreactive capillary mechanism or a sluggish one, effects not only of diets deficient in vitamin but of all the faulty diets resulting in hypermetabolic and hypometabolic activities, all these and many more factors have an influence on the effectiveness of the response of the capillaries to emergencies, which for the purpose of experimentation are bacterial implantations.

The effect of seasons in determining infection has already been mentioned a number of times. The studies of Ruszynak and Beckmann,[378] of Kendall,[379] on intestinal infections and of Brown and Pearce [380] on seasonal variations in experimental syphilis are important, as is that of Wells [381] on differences in rate of growth of bacteria in the animal body, and certain biochemical variations such as those reported by Hess and Lundagen [382] with phosphates, and Maignon and Jung [383] on metabolism of nitrogen.

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375. McDowell, C.: Effect of Different Temperatures and Humidity on Resistance of Rats to Pneumococcus Infection, Am. J. Hyg. **3**:521, 1923.

376. Müller, L.: De l'influence de la témperature sur l'evolution de l'infection charbonneuse, Compt. rend. Soc. de biol. **95**:861, 1926.

377. Schamberg, J. F., and Rule, A. M.: Therapeutic Effect of Hot Baths in Experimental Syphilis in Rabbits, J. A. M. A. **88**:1217 (April 16) 1927.

378. Seasonal Variability of Disease, editorial, J. A. M. A. **80**:476 (Feb. 17) 1923.

379. Kendall, A. I.: Seasonal Recurrence of Intestinal Infections, South. M. J. **8**:120, 1925.

380. Brown, W. H., and Pearce, L.: Animal Resistance and the Endocrine System of the Rabbit in Experimental Syphilis, Proc. Soc. Exper. Biol. & Med. **20**:476, 1923.

381. Wells, W. F.: Seasonal Variation in Multiplication Rate of Micro-Organisms Within the Body, Am. J. Pub. Health **11**:636, 1921.

382. Hess, A. F., and Lundagen, M. A.: Seasonal Tide of Blood Phosphate in Infants, Proc. Soc. Exper. Biol. & Med. **19**:380, 1922.

383. Maignon, F., and Jung, L.: Relation entre l'influence des saisons sur la sensibilité de l'organisme a l'intoxication azotée et l'aptitude de cet organisme a transformer les protéines en graisse, Compt. rend. Soc. de biol. **91**:1390, 1924.

DIET

The particular importance of diet in connection with infection has been much emphasized of late years. The problem of the etiology of scurvy was long complicated by the question of infection. Moore,[384] Daniels, Armstrong and Hutton,[385] who discussed deficiency of vitamin A in relation to nasal sinusitis, and McCollum,[386] who described the pathologic effects of lack of vitamin A and of antirachitic vitamin, have all added to the appreciation of such conditions. In a study of rats on diets deficient in vitamin A Creekmur [387] reported a drying and hardening of the feces; the living bacteria, particularly the streptococci, were found to be decreased in numbers, and he believed that this was due to the unfavorable conditions. However, this does not indicate that the streptococci were fewer in the upper bowel. Findlay [388] showed a definite lowering of resistance to bacteria in scorbutic animals. Werkman [389] found that deficiency in either vitamin A or vitamin B lowered resistance in rats and rabbits to *B. anthracis* and the pneumococcus and that this was not the result of a break in the mechanism that produced antibodies. Werkman, Nelson and Fulmer [390] determined that lack of vitamin C broke the resistance of guinea-pigs to the pneumococcus and *B. anthracis,* and they believed that the primary explanation lay in the accompanying drop in body temperature. They did not find any alteration in the production of agglutinins or phagocytic power. Webster and Pritchett [391] changed the diet of some of their mice from that of the breeding room to McCollum's diet and found that, although both

384. Moore, J. J.: Experimental Studies in Diet Deficiency Diseases, Proc. Inst. M. Chicago **2**:254, 1919.

385. Daniels, A. L.; Armstrong, M. E., and Hutton, M. K.: Nasal Sinusitis Produced by Diets Deficient in Fat-Soluble A Vitamin, J. A. M. A. **81**:828 (Sept. 8) 1923.

386. McCollum, E. V.: Pathologic Effects of Lack of Vitamin A and of Antirachitic Vitamin, J. A. M. A. **81**:894 (Sept. 15) 1923.

387. Creekmur, F.: The Intestinal Bacterial Flora of Rats on a Diet Deficient in Fat Soluble Vitamin A, J. Infect. Dis. **31**:461, 1922.

388. Findlay, G. M.: The Relation of Vitamin C to Bacterial Infection, J. Path. & Bact. **26**:1, 1923.

389. Werkman, C. H.: Immunologic Significance of Vitamins. Influence of the Lack of Vitamins on the Production of Specific Agglutinins, Precipitins, Hemolysins and Bacteriolysins in the Rat, Rabbit and Pigeon, J. Infect. Dis. **32**: 247, 1923.

390. Werkman, C. H.; Nelson, V. E., and Fulmer, E. I.: Immunologic Significance of Vitamins. Influence of Lack of Vitamin C on Resistance of the Guinea-Pig to Bacterial Infection; On Production of Specific Agglutinins and on Opsonic Activity, J. Infect. Dis. **34**:447, 1924.

391. Webster, L. T., and Pritchett, I. W.: Microbic Virulence and Host Susceptibility in Parathyhoid-Enteritidis: Infection of White Mice—Effect of Diet on Host Resistance, J. Exper. Med. **40**:397, 1924.

sets apparently did equally well, the group on the latter diet had a far greater resistance to *B. pestis caviae,* botulinus toxin and mercuric chloride. This is a most important report in regard to animal experimentation. Cramer and Kingsbury [392] stressed the development of infection with avirulent types of bacteria in animals deficient in vitamin A, the local and not the general humoral defense being found diminished. Gross [393] proved that vitamin B contains an antistasis factor and that its absence resulted in intestinal stasis in his rats. He noted cells in the retroileocecal glands which resembled those found to be altered in human colons removed because of advanced stasis. On the other hand, deficiency in vitamin A produced a hurrying through of the contents of the bowel.

In an excellent account of the microscopic changes of rats deficient in vitamin A, Wolbach and Howe,[394] demonstrated alterations in character of the epithelial cells through growth of focal cells in certain parts of the respiratory, alimentary and genito-urinary tract, and they found that the glandular epithelium was also involved. They considered that the specific function of these epithelial cells had been changed so that they became nonsecretory while their growth was increased. Among other conditions, they also found, focal myocardial lesions. They looked on vascularization of the cornea in the absence of infection as a physiologic response to the rapidly growing epithelium. The bearing of such results on the problems of focal infection is obvious.

The work of Plimmer [395] on the relative amounts of the different vitamins, in relation to the other constituents of the food needed to maintain health, is extremely important. He found that different animals did not require the same ratio. A partial (and I wish to emphasize this) deficiency of vitamin B resulted in intestinal stasis which became chronic if the deficiency continued. Grant [396] emphasized that an improper ratio between vitamin C and vitamin D (cod liver oil) increased the permeability of the intestines to bacteria and that an excess of calcium in the diet favored the migration of bacteria into the

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392. Cramer, W., and Kingsbury, A. N.: Local and General Defences Against Infections, and the Effect on Them of Vitamin Deficiency, Brit. J. Exper. Path. **5**:300, 1924.

393. Gross, L.: Effects of Vitamin Deficient Diets on Rats, with Special Reference to the Motor Functions of the Intestinal Tract in Vivo and in Vitro, J. Path. & Bact. **27**:27, 1924.

394. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat Soluble A Vitamin, J. Exper. Med. **42**:753, 1925.

395. New Work on Vitamins, in Miscellany, J. A. M. A. **86**:1156 (April 10) 1926.

396. Grant, A. H.: Effect of the Calcium, Vitamin C—Vitamin D Ratio in Diet on the Permeability of Intestinal Wall to Bacteria, J. Infect. Dis. **39**:502, 1926.

blood. By using a number of diets causing cachexia, Smith and Bogin,[397] were able to produce gangrene in the tails of rats; they attributed the condition to an enfeebled circulation, although intimal changes in the blood vessels were also thought to be contributory. An increase in protein seemed to accelerate the process. It will be clear to all laboratory workers that unless special care is taken, the diet that animals used in the laboratory usually receive is, as a rule, variable and that the increase or decrease in green food according to the season will play an important part in the animals' susceptibility to infection, whether it is experimentally induced or spontaneously acquired.

FATIGUE

Another phase of the general consideration of focal infection is that of fatigue. This has been stressed so often as the determining factor in focal infection that a little space must be given to it. The often quoted statement of Sir James Paget, "You will find that fatigue has a larger share in the promotion or transmission of disease than any other causal condition you can name," finds a ready acceptance in the minds of most persons. However, it is necessary to differentiate various forms of fatigue, for it has a separate meaning to almost every person. Healthy fatigue after intense muscular exercise in the trained athlete, who has a highly developed mechanism for prompt recovery, can scarcely be compared to the fatigue of a sedentary office worker after a hard round of tennis. Moreover, the one has learned the need for care during the period of readjustment and wraps himself up or is massaged, while the other tries to cool off rapidly and thus injures the capillaries by causing an unusual excess of cutaneous reflex contraction. In the first one finds a healthy tonic reaction, in the second, the opportunity is open for infection. It must be realized that during such types of exercise there occurs a general capillary response in most of the body tissues to meet the nutritional demand, and that this response involves mucous membranes and the capillary beds of tonsillar and periapical ulcers and other infected regions. This capillary dilatation favors the entrance of bacteria into the circulation and, if this occurs, the bacteria tend to localize where the capillary stress is greatest or offers the best opportunities for growth.

Oppenheimer and Spaeth[398] found an increase in resistance to subcutaneous injections of tetanus toxin and to intraperitoneal injections of the pneumococcus in rats under the conditions of what I would call

397. Smith, A. H., and Bogin, M.: Experimental Gangrene Produced by Dietary Means, Am. J. Path. **3**:67, 1927.

398. Oppenheimer, E. H. O., and Spaeth, R. A.: Relation Between Fatigue and Susceptibility of Rats Toward a Toxin and an Infection, Am. J. Hyg. **2**:51, 1922.

"healthy" fatigue. Nicholls and Spaeth [399] obtained the same increased resistance in guinea-pigs to pneumococcus but stated that fatigue induced before was much more effective than that induced after the injections. Mellanby [400] showed that the proportions of phosphorus and calcium as well as the fat-soluble vitamins determined muscular activity in young dogs and that this largely depended on the rate of calcification of the bones. Such effects of diet may thus have an indirect effect on induced fatigue. Spaeth [401] found that rats trained by spontaneous daily exercise are less resistant to intraperitoneal injections of pneumococcus than unexercised animals used as controls and brought new evidence of increasing resistance by forced exercise. He found further that this increase in resistance also occurred in guinea-pigs on a reduced diet when the diet caused a loss of weight equal to that found in the exhausted animals, and that in both cases feeding immediately after injection raised the resistance. He believed that this was due to the increase in anabolism. A number of explanations for these phenomena are naturally suggested. The change in circulation in the abdominal cavity following feeding may well raise the resistance to intraperitoneal injections. Further, the decrease in sugar in the blood and tissues under the conditions of the experiments may also raise the resistance by depriving the bacteria of this readily available food supply, but this is probably only one indication of other important metabolic changes.

Nelson, Baldwin, Riggs and Cunningham [402] showed that muscular weakness progressively increased in animals on a diet deficient in vitamin A or vitamin B. Bailey [403] tested the effect of acute fatigue on rabbits and found them more susceptible to intratracheal injections. Chronic fatigue (training) resulted in a lessened susceptibility. The strain in this experimentally produced fatigue was evidently more marked in the respiratory tract. Boycott and Price-Jones [404] worked with rats and used the Gaertner bacillus. They found that fatigue did not have any effect on the mortality after subcutaneous or intraperitoneal injec-

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399. Nicholls, E. E., and Spaeth, R. A.: Relation Between Fatigue and Susceptibility of Guinea-Pigs to Infections of Type I Pneumococcus, Am. J. Hyg. **2**: 527, 1922.

400. Mellanby, E.: Discussion on Nutritional Diseases in Animals, Proc. Roy. Soc. Med. **17**:19, 1924; abstr., J. A. M. A. **83**:617 (Aug. 23) 1924.

401. Spaeth, R. A.: An Experimental Investigation of the Supposed Relation Between Good Physical Condition and Natural Resistance to Infection, Am. J. Hyg. **5**:839, 1925.

402. Nelson, V. E.: Baldwin, F. M.; Riggs, A. G., and Cunningham, M.: Relation of Vitamin Deficiency to Muscle Fatigue, Am. J. Physiol. **72**:69, 1925.

403. Bailey, G. H.: The Effect of Fatigue on the Susceptibility of Rabbits to Intratracheal Injections of Type I Pneumococcus, Am. J. Hyg. **5**:175, 1925.

404. Boycott, A. E., and Price-Jones, C.: Experiments on the Influence of Fatigue on Infection, J. Path. & Bact. **29**:87, 1926.

tions, but they did find a marked difference after feeding the bacillus. In both fatigued and normal rats, the bacillus was found to have migrated to the spleen, but in the former case diarrhea, cyanosis and other signs of illness developed and half of the animals died. By this technic, clear evidence of the deleterious effects of fatigue was shown. Flinn [405] investigated the reputed good effects of acid sodium phosphate in delaying fatigue and concluded that it was due to stimulation of the intestinal tract. It is thus seen that fatigue is of many kinds and that only a careful analysis of the factors involved in experiments in animals permits applying the results of these experiments to the human patient in whom various factors, such as focal infection, faulty diet, constipation and many others, are involved.

I believe that it is clear from the evidence in this review that consideration must be given to a great many underlying conditions affecting the development of infected foci and determining the incidence of systemic infection and the secondary localizations, when such occur. The facts that infections experimentally produced in animals are usually so different from natural infections and that animals are as liable to spontaneous infections as is man make too broad analogies dangerous.

ELECTIVE LOCALIZATION [406]

The hypothesis of elective localization has dominated the interpretation of results of many investigators and in itself has been considered sufficient to account for the localizations in focal infections. The theory is advanced that localization of bacteria in the body depends on inherent differences of a highly specific nature in the bacteria themselves which

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405. Flinn, F. B.: The So-Called Action of Acid Sodium Phosphate in Delaying the Onset of Fatigue, Pub. Health Rep. **41**:1463, 1926.

406. Rosenow, E. C.: Elective Localization of Streptococci, J. A. M. A. **65**:1687 (Nov. 13) 1915; Immunological and Experimental Studies on Pneumococcus and Staphylococcus Endocarditis, J. Infect. Dis. **6**:245, 1909; The Newer Bacteriology of Various Infections as Determined by Special Methods, J. A. M. A. **63**:903 (Sept. 12)) 1914; Iritis and Other Ocular Lesions on Intravenous Injection of Streptococci, J. Infect. Dis. **17**:403, 1915. Rosenow, E. C., and Davis, C. H.: The Bacteriology and Experimental Production of Ovaritis, J. A. M. A. **66**:1175 (April 15) 1916. Rosenow, E. C.: Elective Localization of Bacteria in Diseases of the Nervous System, ibid. **67**:662 (Aug. 26) 1916. Rosenow, E. C.; Towne, E. B., and Von Hess, C. L.: The Elective Localization of Streptococci from Epidemic Poliomyelitis, J. Infect. Dis. **22**:313, 1918. Rosenow, E. C.: Specificity of Streptococci in Etiology of Diseases of the Nervous System, J. A. M. A. **82**:449 (Feb. 9) 1924; Experimental and Clinical Studies on Focal Infection and Elective Localization: Newer Findings and Their Significance, Paper Read Before the Northern Ohio Dental Association, June, 1924; A Bacteriological Study of Pulmonary Embolism, J. Infect, Dis. **40**:389, 1927; Bacteriological Observations on Periodic Ophthalmia in Horses, Proc. Staff Meeting Mayo Clinic **2**:100, 1927.

they have evolved in response to their environment. In the earlier part of this review I have shown that bacterial adaptation plays a long recognized and important rôle in bacterial infection. Early in the history of bacteriology, specificity was practically the only view for explaining the nature of infectious diseases. Robert Koch and his school held the field for many years. It is sometimes forgotten how broad a conception Pasteur had of the problems involved. As one of numerous examples in his studies on chicken cholera he clearly recognized that the spontaneous and experimental infection by the same microbe was different in the guinea-pig, rabbit and chicken. The mere presence of a germ in or on the body was soon found insufficient to explain the occurrence of specific diseases.

Tuberculosis has probably had most influence on making the theory of elective localization seem tenable. *B. tuberculosis* gives a definite type of lesion that is easily produced in experimental animals. It has not been suggested seriously, however, that the bacillus localizes in experimental animals according to the source from which it was obtained in man. *B. tuberculosis* obtained from sputum in pulmonary infections behaves practically the same as that obtained from the spinal fluid in meningitis, the urine in infections of the kidneys or from any other source, and does not show a tendency to locate in the organ or tissue from which it was derived. Certain differences are observed in the distribution of the lesions produced in the various types of animals by the human and bovine strains, but this is readily explained on the basis of difference in virulence, and such phenomena are not to be found in the reports of the supporters of the theory of elective localization. On the contrary, they seem to have found that the species of animal is not important in obtaining their results. Corper and his associates [407] carefully studied this problem of the localization of *B. tuberculosis* in the organs of different animals, and every one should read their series of reports. In the rabbit, the lung showed the greatest involvement and the liver the least; the kidney also often showed lesions. In the guinea-pig the spleen first showed the evidence of tuberculosis, but with larger doses the lungs

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407. Corper, H. J., and Lurie, M. B.: The Variability of Localization of Tuberculosis in the Organs of Different Animals—Quantitative Relations in the Rabbit, Guinea-Pig, Dog and Monkey, Am. Rev. Tuberc. **14**:662, 1926; The Importance of the Distribution of Tubercle Bacilli as Concerns Differences of Susceptibility of the Organs, ibid. **14**:680, 1926. Corper, H. J.; Lurie, M. B., and Uyei, N.: The Importance of the Growth of Tubercle Bacilli as Determined by Gaseous Tension, ibid. **15**:65, 1927. Corper, H. J., and Lurie, M. B.: The Cellular Factor in the Susceptibility of the Various Organs, ibid. **15**:237, 1927. Corper, H. J.; Lurie, M. B., and Uyei, N.: The Significance of Localization and Development of the Bacilli, and of the Cellular Reaction in Man and Animals, ibid. **15**:389, 1927.

developed more lesions than the spleen, the dosage largely determining the relative distribution as did the periods of time at which the animals were studied. The kidney rarely showed involvement in the guinea-pig. The dog is relatively resistant, but differences were not noted between the effects of human and bovine strains. Here, the dose decided the distribution. Corper and his associates further showed that the distribution at various stages after infection depended on the local conditions in the various organs and were based on physicochemical grounds. Quantitative distribution of the bacteria in the organs did not necessarily determine the final number or size of the lesions that developed. Slight changes in oxygen tension were found to be of great importance in the final size and number of the lesions, and the blood supply was therefore considered a most important factor. The hydrogen ion concentration of the blood, as directly influencing the curve of oxygen dissociation, and which increases under conditions of fatigue and starvation, was considered perhaps the most important single factor determining the local growth and activity of the tubercle bacillus. The variability of the cells of the organs in destroying the bacilli was another factor stressed.

It is evident from the foregoing description that the tubercle bacillus itself is not the determining factor in the localization of lesions, except that in this case as in all cases it is a highly aerobic micro-organism. Moreover, the whole success in the treatment of tuberculosis has depended on the treatment of the conditions in the body to prevent the proliferation of one common organism. There is nothing suggesting elective localization in the problem of tuberculosis.

The question of oxygen tension has been particularly stressed by Rosenow as the chief factor to which the streptococci have adapted themselves and in virtue of which adaptation they have taken on the character of electively localizing in various tissues. It would indeed be strange if the conditions determining the oxygen tension as outlined by Corper and the variations in these in the different animal species did not have any bearing on elective localization with streptococci. If one judges from the reports published by Rosenow, all animal species have apparently the same conditions of oxygen tension in analogous organs and tissues. It is true that in his earlier work Rosenow recognized a number of factors, such as cold, in changing these conditions, but with the development of his theory these factors took a minor part and were largely neglected. As an illustration of this, I will give a brief history of a micro-organism (no. 734) studied by Rosenow for its effects on animals. This history is abbreviated from a number of his reports.

On Jan. 27, 1913, the micro-organism was isolated from the joint of a patient with acute articular rheumatism. It produced long chains, greening on blood agar and failed to ferment mannit or inulin. On January 29 the growth from 25 cc. on intravenous injection killed a rabbit in five days. On February 11, the growth from

30 cc. killed a rabbit in one day, and the growth from 30 cc., after three animal passages, killed a rabbit in six days. On February 13, the growth from 35 cc., after two animal passages, killed a rabbit in one day. On the same day, aerobic cultures were made in distilled water, and on March 1 eleven colonies of hemolyzing streptococci were obtained which fermented mannit. On March 5, the growth from 40 cc., after eight animal passages, failed in two days to kill a rabbit. It was given a second injection and died the next day. On March 10, the growth from 45 cc. of this strain, "after it was made to resemble the strains from muscular rheumatism," killed a rabbit in two days. Rosenow said that the virulence was distinctly greater than before the transmutation. The foregoing record did not contain evidence of this. Lesions of the stomach were not reported in any of these rabbits. On March 13, the growth from 300 cc., after ten animal passages (I presume the foregoing record contains reports of the animal passages), did not kill a small dog after four weeks. This dog was chloroformed on April 10, and loose teeth and osteomyelitis of the lower jaw, localized adhesive pleuritis, white streaks in some muscles, a suppurating sinus lying between the muscle sheaths near the wrist, (presumably at the site of the joint from which fluid had been aspirated) and a large, round ulcer in the duodenum were found. This animal had developed severe double conjunctivitis and arthritis, was ill almost all the time, had lost weight and had eaten little. When one appreciates the comparative ease with which ulcers develop in dogs and the fact that this culture had never formed ulcers in rabbits, the result does not appear to be significant. This strain (734) as isolated was transformed into a typical pneumococcus after eleven passages. Was the dog that received the tenth passage culture the eleventh dog? If so, could not the pneumococcus have come from the pleuritis, for instance? In another report,[196] a dog injected thirteen weeks previously, died of distemper and had a duodenal ulcer. Another also died of distemper more than fourteen weeks after the injection; it, also, had a duodenal ulcer. These animals given as examples are, I presume, included in the tables on elective localization.

In his report on herpes zoster, Rosenow [408] gave details of his experiments, and many interesting things are to be noted. A strain of streptococcus from a patient's tonsils injected into six dogs gave four positive and two negative results, while ten rabbits with the same culture gave six negative and four positive results. The total results of this study showed; 27 dogs were injected with various strains, and in these 17 results were positive and 10 were negative; 60 rabbits, half of which were positive and half negative, and 14 guinea-pigs, 11 of which were positive and 3 negative. The animals recorded in the text gave a total of 101, while the table showing data of elective localization included only 83. Such a wide difference in figures would disturb the percentage obtained.

In a report on appendicitis, Rosenow [175] used 29 strains from the tonsils and 30 strains from the appendix, either pure or mixed with fusiform bacilli. This was published before his article on elective localization. He recorded that streptococci from the wall of the appendix

408. Rosenow, E. C., and Oftedal, S.: The Etiology and Experimental Production of Herpes Zoster, J. Infect. Dis. **18**:477, 1916.

injected into eight rabbits gave lesions of the gallbladder in three rabbits; in table 5 of the same article, a strain from the tonsils and one from the peritoneal coat are listed as involving the gallbladder, making a total of five positive results with strains at isolation (including, as Rosenow said, "the first animal passage"), while in the table of the report on elective localization in 1915, the number of animals with a lesion of the gallbladder is only given as one. In his article published in 1913 on ulcer of the stomach, Rosenow reports strains from patients with rheumatic fever after animal passages. Eighteen rabbits were injected after from two to five passages, eight after from five to ten passages and one dog after ten passages. Nevertheless, in the table in the article on elective localization, only nineteen animals are given under the heading of "Rheumatic Fever Strains After Animal Passage." Another interesting inclusion in this table was the work on erythema nodosum [409] with a diphtheroid bacillus, which at times was pleomorphic and resembled streptococci.

Many more instances could be cited of such a confusing use of figures, so that it is impossible to learn what animals are included in the tables and what are not. Rosenow made a number of comments in different papers which are of particular importance. "No special attention was paid to the diet of the animals" appeared in the 1916 article on gastric and duodenal ulcer.[106] He stated that young animals showed different susceptibilities in herpes zoster, ulcer of the stomach and chorea but his table showed no comparative results. The probability of secondary infections with streptococci from the animals themselves apparently did not occur to Rosenow. Seasonal variation in animal resistance is suggested in a number of the reports such as that on epidemic appendicitis and parotitis,[175] but it is not so interpreted. The number of bacteria injected varied greatly. In the paper on elective localization, the doses given are: for rabbits, from 7.5 to 45 cc. and for dogs, from 15 to 75 cc. However, although Rosenow stated that the number of lesions in muscles was in proportion to the size of the dose injected, one finds in his articles on rheumatism the description of a rabbit that received 75 cc. and a dog, 240 cc. In the paper on ulcer of the stomach, a dog was given 300 cc., in the report on erythema nodosum, a dog was given 150 cc and in the report on herpes zoster, a rabbit was given 60 cc. and dogs, 90 cc. Also, much smaller doses than those included as the minimum were often used. The number of injections also varied, and notwithstanding his own observations on sensitization, Rosenow reported rabbits as having been injected once, twice, three and four times. The periods between injection and death were variable, lasting from ten minutes up to twenty-eight days. All the evidence on

409. Rosenow, E. C.: The Etiology and Experimental Production of Erythema Nodosum, J. Infect. Dis. **16**:367, 1915.

experimental bacteremia favors the view that the early primary distribution may not be the same as that occurring after definite infections have been established. In the various reports of Rosenow, such data have not been tabulated.

Of particular interest would be the complete separation of the results obtained with bacteria isolated from the actual site of infection and those obtained with the bacteria from the supposed atrium of invasion. For example, Rosenow made one culture from the spinal fluid of a patient with herpes, and a detailed account is not given of the results with this most important strain. The great mass of the experiments were with cultures from the oral cavity.

Another important requirement to make such work of value is that each strain should be injected into the same number of animals. The importance of this point has been well illustrated in the work of McMeans [410] on chronic suppurative arthritis. He injected thirty-four rabbits with *Streptococcus pyogenes* from an abscess of the submaxillary gland in a patient who had never had arthritis and found that purulent arthritis occurred in all his animals. In order to overcome these thirty-four positive results the advocates of elective localization would require first, thirty-four animals which gave positive reactions after injection with a streptococcus from a patient with arthritis and second, a series of thirty-four groups of animals with a number of other arthritic strains before the evidence would appear to demonstrate the type of elective localization under discussion. Further, all streptococci not showing evidence of any localization should be disregarded, as in this problem I am primarily studying localization. The frequently quoted last line of Rosenow's table with the results of five "Lab." strains on 100 animals show such a lack of localizing power, and it is illogical to contrast these results with those obtained with more virulent and pathogenic strains.

It is impossible to evaluate the personal equation in such work, and one cannot determine whether the same meticulous care was exercised in discovering localization by looking for areas of reaction, hemorrhage of the capillaries or other evidence in all parts of the body in all animals. For example, the nervous system is not included in the tables in any of the early reports.

Every investigator agrees that the technic in animal experimentation is at best only a crude method for obtaining conditions at all comparable to the natural conditions of infection. The shock of heavy intravenous injections, the sensitization or resistance with repeated injections, the primary localization in all organs, and the later localization in certain tissues, these and many other conditions must be considered.

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410. McMeans, J. W.: Experimental Chronic Suppurative Arthritis, Am. J. M. Sc. **160**:417, 1920.

I believe that the proper basis on which to obtain the significance of these results is to determine the total number of animals showing a particular lesion and then to estimate the percentage of such lesions apparently induced by the so-called "specific" and "nonspecific" strains. I therefore did this at the time of the early publications on this subject so that I might learn how important the evidence really was. The results

A Rearrangement of Rosenow's Results Showing Number of Animals with various Lesions and the Percentage of These Lesions Following the Injection of "Specific" and "Nonspecific" Strains of Streptococci

Number and Percentage of Animals Showing Various Lesions	Time of Testing Strains and Number Showing Lesions: At Isolation	After Animal Later Passage		Totals
1. Lesions of the Joints				
Number of animals affected	131	28	37	196
Percentage with strains from patients with rheumatic fever	36	11	19	29
Percentage with other strains	64	89	81	71
2. Endocardial Lesions				
Number of animals affected	122	17	21	160
Percentage with strains from patients with endocarditis	30	..	..	23
Percentage with strains from patients with rheumatic fever	27	18	48	29
Percentage with other strains	42	82	52	48
3. Myocardial Lesions				
Number of animals affected	82	11	16	109
Percentage with strains from patients with rheumatic fever	38	36	44	39
Percentage with strains from patients with myositis	17	..	..	13
Percentage with other strains	44	64	56	48
4. Lesions of the Muscles				
Number of animals affected	78	13	19	110
Percentage with strains from patients with rheumatic fever	24	0	16	20
Percentage with strains from patients with myositis	38	..	..	27
Percentage with other strains	37	100	84	53
5. Stomach and Duodenal Lesions with Hemorrhages				
Number of animals affected	130	16	36	182
Percentage with strains from patients with ulcer of stomach	48	6	25	40
Percentage with other strains	52	94	75	60
6. Stomach and Duodenal Lesions with Ulcer				
Number of animals affected	92	10	27	129
Percentage with strains from patients with ulcer of stomach	67	0	48	58
Percentage with other strains	33	100	52	42
7. Lesions of the Gallbladder				
Number of animals affected	76	5	38	119
Percentage with strains from patients with cholecystitis	43	20	24	36
Percentage with other strains	57	80	76	64
8. Appendical Lesions				
Number of animals affected	65	8	14	87
Percentage with strains from patients with appendicitis	71	50	71	69
Percentage with other strains	29	50	29	31
9. Lesions of Kidneys				
Number of animals affected	54	5	16	75
Percentage with strains from patients with rheumatic fever	52	60	50	52
Percentage with other strains	48	40	50	48

are shown in the accompanying table, which is made up from Rosenow's table of elective localization of 1915. The observations made on the five "Lab." strains have not been included for the reason given.

It will be noted that the animals showed lesions in the following order: joints, 131; hemorrhages in the stomach and duodenum, 130; endocardium, 122; ulcers in the stomach and duodenum, 92; myocardium, 82; muscles, 78; gallbladder, 76; appendix, 65; and kidney, 54.

It will be recalled that Henrici,[411] in his own experiments, found that 65 per cent of his animals that had been injected with nonhemolytic streptococci showed lesions or died following the injection. The order of localization of the lesions was: joints, 30 per cent; myocardium, 24 per cent; kidney, 18 per cent; muscles, 15 per cent; endocardium, 9 per cent. With the hemolytic streptococci, 75 per cent of the animals became infected, and the order of involvement was: joints, 26 per cent; myocardium, 25 per cent; kidney, 24 per cent; muscles, 13 per cent; endocardium, 11 per cent.

In one report, McMeans [110] paid particular attention to gastric lesions and obtained, with various streptococci, the following order of lesions: stomach, endocardium, myocardium, appendix, joints, duodenum, small intestine, muscle and kidney; in his study on bacteremia,[320] there was only a slight change in the order. Similar lists could be arranged from the results of Haden,[412] Nickel,[413] Topley and Weir [414] and from many other reports in which such details are given. Sometimes one organ or tissue is first in order, sometimes another, but so many factors are involved that this is to be expected.

The ease with which this character that determines the elective localization of streptococci can be changed is an important corollary of all this work. In some cases, one must inject the microbes directly from the human focus, not waiting for isolation; in another case, the microbes are retained for many years in media or after transport in milk and dairy products. Forssner [251] believed that his adaptation of streptococci to kidney tissue was of a fleeting character and could disappear rapidly even in the circulating blood. Unfortunately, he paid chief attention to involvement of the liver, spleen and kidneys. Forssner had great difficulty in adapting his hemolytic streptococcus to growth in kidney extracts, but this was at last accomplished by incubating the kidney of

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411. Henrici, A. T.: The Specificity of Streptococci, J. Infect. Dis. **19**:572, 1916.

412. Haden, R. L.: Elective Localization in the Eye of Bacteria from Infected Teeth, Arch. Int. Med. **32**:828 (Dec.) 1923. Haden, R. L., and Jordan, W. H.: Multiple Onychia as a Manifestation of Focal Infection, Arch. Dermat. & Syph. **8**:31 (July) 1923. Haden, R. L.: Lesions in Rabbits Following the Intravenous Injection of Bacteria from Chronic Periapical Dental Infections, Am. J. M. Sc. **172**:885, 1926; Elective Localization of Streptococci, Southern. M. J. **19**:253, 1926; Experimental Evidence of the Relation of Dental Infection to Systemic Disease, M. J. & Record **123**:783, 1926. The Elective Localization of Bacteria in Heart and Vascular Disease, J. Lab. & Clin. Med. **12**:31, 1926.

413. Nickel, A. C.; The Localization in Animals of Bacteria Isolated from Foci of Infection, J. A. M. A. **87**:1117 (Oct. 2) 1926.

414. Topley, W. W. C., and Weir, H. B.: The Lesions Produced in Rabbits by the Inoculation of Streptococci Isolated from Rheumatic and Other Lesions in the Human Subject, J. Path. & Bact. **24**:333, 1921.

an infected rabbit and after twenty-four hours, emulsifying the organ. The streptococcus had lost its hemolytic power, and the evidence would suggest that he had picked up an animal strain. The dosage of cocci injected from these luxuriant growths was of course greatly increased over the poorly growing "original" strain.

Throughout all of this work on elective localization, there is a tendency, often evident, to consider a strain of streptococcus specific ex post facto after some chance result and that when this result is absent, the strain again reverts to the nonspecific group. I think it is evident that streptococci can cause certain lesions throughout the animal body, but that it is roughly a 50 per cent chance whether any particular localization occurs with a "specific" or "nonspecific" strain.

I will not attempt to give a complete list of the various workers opposed to this theory nor those in favor of it. Kuczynski and Wolff [20] could not confirm Forssner's results, and many investigators have failed to substantiate Rosenow's work. It would take too much space to review all the work on both sides, but I have endeavored to develop the important principles involved.

The most important thing to be noted in practically all the work is the absence of strict adherence to the one point of interest: Does the localization of bacteria such as streptococci depend on an inherent property in the micro-organism which is independent of, or which is demonstrable in spite of alterations of technic or varying susceptibilities due to different species of animals, the effects of diet, previous or concurrent spontaneous infection, age, and a variety of environmental conditions? Each possible factor must be controlled independently, and it is a difficult undertaking.

The conclusion to be drawn from the reports available is that elective localization as a hypothesis to explain the occurrence and incidence of focal infection as it is found in man is insufficient. However, what Rosenow and his followers particularly showed and what all the other investigators of the problem have definitely demonstrated is that streptococci do localize in various organs and tissues and can produce lesions at least sufficiently suggestive of those found in man so that their potential danger in infected foci cannot be neglected.

CONCLUSIONS

1. Focal infection is a principle of infection of great importance in numerous disease conditions in man.

2. The factors determining the localization of bacteria which have entered the blood stream are those which alter the circulation and thereby the nutrition of the cells of the tissues, particularly the endothelium of the capillaries.

3. The factors determining the invasion of bacteria from an infected focus are largely dependent on the local circulation about and in the focus and the relative quiescence or movement of the tissues. Dilatation of capillaries tends to facilitate such an invasion but sluggish circulation may permit the more invasive types of microbes, such as streptococci, to grow through or to produce local thrombi in the smaller vessels. The survival of these invading bacteria depends on their virulence (rate of growth) and on the inherent ability of the endothelial cells in a given organ to destroy them. The amount of damage resulting from virulent bacterial infections depends both on the pathogenicity of the parasite and on the resisting mechanism of the host.

4. When a focus of infection is discovered and is considered responsible for a disease condition elsewhere, it requires the highest type of diagnostic ability to prove that this is true. The cure of the patient after removal or treatment of a suspected focus is generally considered the most convincing evidence that the focus was the source of the infection. However, such an outcome may be due to a general tonic stimulus resulting from the removal of one cause of a lowered systemic resistance. Failure to effect a cure by these means may indicate that the focus is not the cause, or that the secondary focus is well established and the damage done irreparable.

5. The specificity of the bacteria involved has not been proved, and the evidence favoring the theory of elective localization is so open to misinterpretation and so limited in its practical application that it cannot be considered as a help in the solution of the problem. A certain general bacterial adaptation to environment is accepted by every one, but the factors on the side of the host are more variable and are far more important. This has been well demonstrated in tuberculosis, and, from what is known of the types of infection that have been discussed in this review, this way of approach seems most hopeful.

6. The standards set by investigators in the studies on vitamin deficiency, heredity and malignant tumors should be followed by bacteriologists in experimental infections in animals, and a technic more closely approaching natural conditions must be standardized before satisfactory results can be attained.

Notes and News

University News, Promotions, Resignations, Appointments and Elections.—At the State University of Iowa, B. E. Clarke and H. D. Palmer have been promoted to assistant professor of pathology and bacteriology; B. E. Konwaler has been appointed instructor and J. P. Clark and W. B. Armstrong, assistants; Lillian Greer has resigned as instructor in bacteriology. The new medical laboratory building is now practically in full operation. The division of space, is approximately; the first floor, pathology and bacteriology; second floor, physiology, preventive medicine and hygiene; third floor, pharmacology and anatomy, and the top floor, housing of animals and rooms for operating on animals. It is the hope that the new hospital building now under construction will be occupied by September, 1928.

G. A. Bennett, assistant in pathology and bacteriology in the University of Iowa, has been appointed resident pathologist in the Peter Bent Brigham Hospital, Boston, and instructor in pathology in the Harvard Medical School.

Dr. Andrew W. Sellards, assistant professor of tropical medicine at the Harvard Medical School, has been granted leave of absence for the academic year 1927-1928 and will go to West Africa to study yellow fever and other tropical diseases.

Orin A. Ogilvie has been made assistant professor of anatomy and pathology in the University of Utah.

At Vanderbilt University, Nashville, Tenn., Charles E. Woodruff, assistant in pathology at Yale University, has been appointed instructor in pathology and Wieland W. Rogers, assistant in pathology.

Thurman B. Price has been appointed associate professor of bacteriology and public health and Frank Forry associate professor of pathology at the Indiana University School of Medicine, Indianapolis.

Ross Buzzanca has been made instructor in pathology and bacteriology in the University of Alabama.

At Tulane University, New Orleans, Roy F. Feemster and O. M. Larimore have been appointed assistants in the department of pathology and bacteriology; and E. H. Lawson, pathologist to the Southern Baptist Hospital in New Orleans, has been made instructor.

Thomas J. Lasser has been made assistant in pathology in the University of Georgia.

Ferdinand C. Helwig has been promoted to associate professor in pathology in the University of Kansas.

At Johns Hopkins University, Johnson McGuire has been appointed assistant in pathology and Samuel S. Blackman, assistant in surgical pathology.

Tom Hare, of the Lister Institute of Preventive Medicine, has been appointed professor of pathology in the Royal Veterinary College, London.

H. Zangger, formerly professor of forensic medicine in the University of Zurich, has been appointed to a similar post in Berlin and to the directorship of Unterrichtsanstalt für Statsarzneikunde und Institut für gerichtliche Medizin.

Louis A. Braafladt, professor of pathology in Shantung Christian University, Tsinan, Shantung, China, is now pathologist to Trinity Hospital, Minot, North Dakota.

Leo Bleyer, assistant in the Hygienic Institute at Basel, has been appointed director of the pathology and bacteriology of Marquette University, Milwaukee.

A New Medical Martyr to Science.—Adrian Stokes, aged 41, professor of pathology at Guy's Hospital, London, has died of yellow fever contracted while investigating that disease. He was a grandson of the illustrious William Stokes (1804-1878), and received his education at Trinity College in Dublin, where he served as professor of bacteriology from the close of the war until 1922, when he was called to London. During the war, he was a member of the army medical corps and displayed a remarkable energy and ingenuity. He devised the method of administering oxygen by nasal catheter in cases of gassing, and did much valuable work on gas gangrene, dysentery, infections from wounds and spirochetal jaundice, which he traced to infection from rats running over the food for the soldiers in the trenches.

Study of Ascariasis.—The American Child Health Association has made a grant for an extended investigation of ascariasis in children in the United States. The work will be conducted under the direction of Prof. W. W. Cort, professor of helminthology in the Johns Hopkins University, under the auspices of the division of medical sciences, National Research Council, through its committee on medical problems of animal parasitology.

Movement to Standardize Laboratory Procedures.—It is reported that the cooperation of the medical profession is requested by the newly organized New York Association of Diagnostic Laboratories in the creation of a research laboratory for the purpose of standardizing methods and procedures of diagnostic laboratories. Among the other objects of the organization are the elevation of the standards of diagnostic laboratories and the establishment of a closer relationship between the medical and allied professions.

New Laboratory Building of the Western Pennsylvania Hospital, Pittsburgh.—This building has been opened with appropriate ceremonies. Ralph R. Melon, formerly pathologist to Highland Hospital, Rochester, N. Y., is the director; Kurt Semsroth is in charge of pathology, Robert Koch, of bacteriology, and H. D. McClugage, of biochemistry.

Death of Gruber.—Max von Gruber, successor to Pettenkoffer as director of the Hygienic Institute in Munich, died recently. He will be remembered for his pioneer work on agglutination. In 1896, in conjunction with Durham, he described specific agglutination of typhoid bacilli and clearly pointed out its diagnostic significance.

Abstracts from Current Literature

Pathologic Physiology

Effect of Parathyroid Hormone on Blood Coagulability. Leo M. Zimmerman, Am. J. M. Sc. **174**:379, 1927.

An increase of calcium in the blood by injecting parathyroid hormone did not affect constantly the coagulation time in normal or icteric persons or animals.

On the Existence of a Parathyroid Hormone. F. T. Jung, Am. J. Physiol. **82**:22, 1927.

Following the implantation of the parathyroid glands of cats and dogs into parathyroidectomized rats, a slight but definite mitigation of symptoms occurred. Since survival of the implants was unlikely under experimental conditions, it is concluded that the parathyroids contain a store of hormone; this is not species specific, is not a chemical artefact and was not present in the control tissues used.

H. E. Eggers.

The Effect of the Pericardium on Cardiac Distention by the X-Ray. J. A. Wilson and W. J. Meek, Am. J. Physiol. **82**:34, 1927.

It was found that with low venous pressures (from 4 to 0 cm. of water) there was an apparent restraining action on cardiac dilatation in the dog, which was due to the tonus of the diaphragm exerted through the pericardium by means of the pericardiodiaphragmatic attachments.

With these attachments cut, the first restraining action of the pericardium proper was manifested at a venous pressure of 0 cm. of water, and reached an appreciable magnitude at 2 cm. When the pressure was increased this restraint also became greater until the heart filled the pericardial cavity, where it became more and more apparent with farther increases in pressure.

The heart completely filled the pericardium at a venous pressure of about 8 cm. of water, or at an effective venous pressure of from 15 to 16 cm. of water measured venous pressure plus 8 cm. of negative intrathoracic pressure.

H. E. Eggers.

Studies on Absorption from Serous Cavities. R. S. Cunningham, Am. J. Physiol. **82**:59, 1927.

The diaphragmatic lymphatic drainage in rats was occluded by two procedures: by ligating the anterior group of lymph vessels by means of a ligature passed around the sternum and drawn tight, and by free dissection and ligation of the tissues surrounding the aorta. Both procedures were resorted to in some of the animals. In spite of lymphatic occlusion produced in these ways, there was no evidence of any effect on the absorption from the peritoneal cavity of isotonic solutions; hence, the author concludes that such absorption takes place through the vascular system of the blood.

H. E. Eggers.

The Influence of High Systemic Blood Pressures on the Right Ventricle and Pulmonary Circuit. L. N. Katz and C. J. Wiggers, Am. J. Physiol. **82**:91, 1927.

Pressure curves, recorded on intact animals (dogs), showed the following results due to mechanical compression of the thoracic aorta: During the first few systoles following the compression, the small volume of residual blood

caused a slight initial elevation of left ventricular pressure, and usually a slight increase of intra-auricular diastolic pressure. These changes were without effect on the pulmonary arterial pressure; the diastolic pressure here remained unchanged so long as the heart rate was constant; it fell when this became slower. The reduced flow through the inferior vena cava often appeared to be overbalanced by the greater flow of blood through the coronary and other collateral circuits. A slight increase in right auricular diastolic and right ventricular initial pressures resulted. From this there followed a slight increase in the isometric gradient of the ventricular contraction, a somewhat higher systolic summit and a frequently present elevation of pulmonary systolic pressure. The changes, however, were all so slight that they required a sensitive apparatus for their detection.

H. E. EGGERS.

ALTERATIONS IN THE PERMEABILITY OF SKIN CAPILLARIES DURING THE COURSE OF TUBERCULOSIS. SAMUEL A. LEVINSON and WILLIAM F. PETERSEN, Am. Rev. Tuberc. **15**:681, 1927.

By means of the blister method, definite alterations in capillary permeability and the inflammatory response of the skin can be determined in different clinical stages of tuberculosis. Capillary permeability remains practically constant in the "incipient" and "moderately advanced" stages, but the blister time becomes prolonged and the "inflammatory index" consequently smaller. In the "far advanced" stage, there is a progressive increase in the capillary permeability and a shortening of the blister time. The latter condition is believed to be associated with an increased parasympathetic status of the vegetative system. In exudative cases the permeability is markedly increased. Examined on the basis of the duration of the disease, those instances of longest duration have the lowest index of permeability and the lowest inflammatory index. Any relation between this response to cantharides and the tuberculin reaction is not evident. The lowered resistance incident to season, menstruation and parturition is associated with the change in the vegetative status of the organism (parasympathetic), of which the change in permeability is a manifestation. On the other hand, the increase in resistance (relative benignancy), demonstrated for senility and for arteriosclerotic nephritis, may be associated with the relatively sympathetic status of such persons.

H. J. CORPER.

INFLUENCE OF THE LIVER ON TOXICITY OF BILE. E. C. DAVIDSON and W. C. EMERSON, Arch. Surg. **15**:57, 1927.

Bile was injected into the portal and systemic system but evidence of any action of the liver on the bile was not obtained. The serum calcium rose rapidly and the animals developed cardiac arrhythmia. Death is believed to be due to the direct action of the bile on the myocardium.

N. ENZER.

CHANGES IN THE BLOOD FOLLOWING OPERATION. E. V. ALLEN, Arch. Surg. **15**:254, 1927.

The erythrocyte and leukocyte counts showed a constant sharp postoperative increase. Prothrombin, fibrinogen and lipoids also showed constant rise. The increase in these constituents of the blood, all of which play some part in blood coagulation, undoubtedly favors intravascular clotting.

N. ENZER.

PREDISPOSITION AND NUTRITION. TADASEA SAIKI, Ann. de l'Inst. Pasteur **41**:668, 1927.

Guinea-pigs and rats fed on diets deficient in vitamin A, B and C are more resistant to strychnine than are normal animals. A regimen deficient in vitamin A and rich in calcium phosphorus produces bladder, kidney and gallstones in rats. By means of roentgen-ray examinations cures were noted in

six rats with stones after a diet rich in vitamin A was fed. Rats kept alive over long periods of time with a minimum vitamin A diet were found to develop typical squamous cell carcinoma of the stomach and bladder with lesser changes in other organs, one rat showing metastasis of the lung. Local irritation was not used and evidence of ulcers was not found. In relation to the formation of cancerous growth the cicatrization of wounds was noted under various vitamin regimens, and it was found that a diet deficient in vitamin A favored healing or proliferation of epithelial tissue.

G. B. RHODES.

STUDIES ON RESPIRATION UNDER INCREASED AIR PRESSURE. A. ANTHONY, Beitr. z. Klin. d. Tuberk. **66**:340, 1927.

Studies on healthy and diseased persons showed that an increase in air pressure does not alter the gaseous metabolism, respiratory volume, the respiratory frequency, nor the vital capacity. Healthy persons show at certain phases a decrease of ventilation, while in asthmatic patients an increase in ventilation occurs. Under increased air pressure the respiration is more quiet and shows a tendency to be deeper. These alterations cannot be explained on a purely mechanical basis. It is assumed that the increase in air pressure acts as a stimulus on the organism which is manifest in part by the alterations of the respiration. The therapeutic results in the pneumatic chamber are explained by this theory.

MAX PINNER.

MOTILITY OF THE APPENDIX. R. RÖSSLE, Beitr. z. path. Anat. u. z. allg. Path. **77**:121, 1927.

In the controversy between Aschoff and Ricker over the pathogenesis of appendicitis, Rössle takes a stand with Ricker, who considered the primary factor in appendicitis to be a disturbance of motility or an abnormality in neurovascular function leading to localized necrosis, to which infection is secondary. Ruf, working in Aschoff's laboratory, had claimed that the appendix never exhibits any peristaltic activity and that this factor could not have the importance in the pathogenesis of appendicitis which Ricker had claimed for it. Rössle maintains that it is easy to discern the peristaltic activity of the appendix left in Ringer's solution, the peristalsis sometimes being spontaneous, and at other times elicited only after mechanical, chemical or electrical stimulation. Peristalsis is necessary for the normal evacuation of the appendix, the stasis which results from deficient or absent activity helping to initiate infection. Rössle ends his polemic with the famous words of Gallileo, after the latter had been cast into prison, "But it does move," which words happen to have been the title of the abstractor's high-school graduation oration, now long since more completely forgotten than Gallileo's original words and almost as completely forgotten as will be the controversy over the motility of the appendix in a few years.

O. T. SCHULTZ.

RESPIRATION OF LIVER TISSUE. W. GROSS and C. NEUHAUS, Beitr. z. path. Anat. u. z. allg. Path. **77**:304, 1927.

Gross and Neuhaus studied the cellular respiration of liver tissue of rats by the method of Warburg, with the aim of determining whether stored materials enter into the cellular activity. Rats under normal dietary conditions, others subjected to undernutrition, and still others subjected to rich diet for seven day periods previous to examination were used. The results are expressed as the quotient obtained by dividing the cubic millimeters of oxygen utilized per hour by the milligrams of dried tissue. For the normal controls the figure varied from 8.2 to 12.5, with an average of 10.18, the variation presumably being due to the amount of nonliving material stored within the cell under control conditions. For the starvation series the figures varied from 9.7 to

18.7, the average being 13.6, a slight but definite increase. In the overfed series the figure varied from 10.4 to 12.4, with an average of 11.3. The addition of dextrose to the Ringer's solution did not increase the tissue respiration.

O. T. SCHULTZ.

Pathologic Anatomy

ACTINOMYCOSIS OF THE VERTEBRAE (ACTINOMYCOTIC POTT'S DISEASE). W. M. SIMPSON and C. A. MCINTOSH, Arch. Surg. **14**:1166, 1927.

Four cases are described in all of which a clinical diagnosis of tuberculosis of the spine was made. The authors point out that there is a distinct difference in the roentgenograms of the two conditions. The characteristic lesion of actinomycosis of the vertebrae is erosion of the central portion of the bone. The process generally begins as a periostitis secondary to some distant focus and involved by spreading sinuses and abscesses. The periosteum becomes elevated, and the cortex of the bone is attacked. Tuberculosis, on the other hand, characteristically attacks the inner portion of the body near the disk, and ultimately leads to collapse of the body and angular deformity. In actinomycosis the spinous and transverse processes are also involved, whereas they are generally free in tuberculosis. Perivertebral phlegmon with multiple burrowing sinuses and abscesses is characteristic, and these eventually reach the skin and discharge the creamy-yellow pus in which the fungi are found, unless a secondary infection obscures them. The presence of vascular granulation tissue containing large lipoid-filled cells and much coarse interlacing hyaline connective tissue should stimulate a search for the ray fungus.

The primary lesion in two of the cases was in the lungs, and in the other two in the appendix or in the region of the appendix. Renal, cerebral and hepatic metastatic abscesses were found, but the process develops essentially by extension.

N. ENZER.

SARCOMA COMPLICATING PAGET'S DISEASE OF THE BONE. C. E. BIRD, Arch. Surg. **14**:1187, 1927.

In sixty-four cases of Paget's disease of the bones found in the records of the Boston hospitals, six cases of sarcoma of one of the involved bones occurred, and three similar ones were found in the Bone Registry. These were all fibrosarcomas with varying degrees of bone formation. The average age of the patient at the onset of the symptoms of tumor was 57 years. This high incidence of sarcoma in Paget's disease is significant, especially when the fact that sarcoma of the bone is a disease chiefly of youth is remembered.

N. ENZER.

PREVENTION OF REGENERATION OF THE RIBS. A PROBLEM IN THORACIC SURGERY. J. R. HEAD, Arch. Surg. **14**:1209, 1927.

In many multiple stage operations, regeneration of the resected ribs gives rise to considerable difficulty. Experiments were conducted to determine a means of preventing this regeneration by chemical cauterization of the periosteum. Cauterization with concentrated chromic acid and Zenker's solution gave satisfactory results and did not cause perforation of the pleura. Zenker's solution was more satisfactory than the chromic acid.

N. ENZER.

SARCOMA OF THE OMENTUM. A. L. MCDONALD, Arch. Surg. **14**:1245, 1927.

The author reports a case of primary sarcoma of the omentum and gives an excellent review of the literature. About fifty cases are on record. If a tumor is to be classified as a sarcoma of the omentum, it must fulfil three

requirements: It must be a localized tumor within the omentum, unattached to other structures; it must be histologically a sarcoma, and it must recur or metastasize. The absence of recurrence or metastases will throw doubt on the diagnosis despite the histologic picture. N. ENZER.

FIBROMA OF THE INTESTINES. HARRY C. CLIFTON and BENEDICT B. LANDRY, Boston M. & S. J. **197**:8, 1927.

A case of fibroma of the ileum associated with intussusception is reported and an attempt made to tabulate all cases of fibroma of the intestines thus far reported. Forty-five cases were found in the literature, the majority being in the small intestine. The most frequent symptom of these tumors is intussusception.

HEART LESIONS PRODUCED BY THE DEEP X-RAY. F. W. HARTMAN, ADOLPH BOLLIGER, H. P. DOUB and F. JANNEY SMITH, Bull. Johns Hopkins Hosp. **41**:36, 1927.

The effect of carefully measured irradiation on the heart of the experimental animal (sheep, dog) has been studied clinically and pathologically. If the dosage is sufficient, either in a single massive or in often repeated smaller applications, certain characteristic pathologic changes are brought about in the heart. The gross changes are as follows: (*a*) hydropericardium, (*b*) hemorrhagic infiltration of the right auricle, especially of the right auricular appendage, (*c*) more rarely, after heavy dosage has been projected through the side, there is thickening and hyaline degeneration of the epicardium with hemorrhagic infiltration of the ventricular walls and (*d*) at autopsy these animals show passive congestion of the viscera. Certain characteristic microscopic changes in the heart have been described: (*a*) in the auricular myocardium, (*b*) in the ventricular myocardium and (*c*) in the His' bundle of the sheep. These microscopic myocardial changes vary with the acuteness or chronicity of the lesions produced. The records are presented of patients who were given relatively large amounts of deep roentgen-ray treatment over the cardiac area as a therapeutic measure for tumors of the mediastinum or lung, and who later came to autopsy. Microscopic sections of the myocardium from these patients show changes which are comparable to those found in the experimental animal following exposure to the roentgen ray, but the terminal infection in the first and third cases and the age of the second patient may have a bearing on the observations. Electrocardiographic records made from the different dogs used in the experiments reported showed a variety of deviations from the normal, more noteworthy changes being: (*a*) inversion of T in leads I and II and frequently in III as well and certain abnormal forms of T; (*b*) paroxysmal tachycardia; (*c*) auricular flutter was recorded in four animals; (*d*) auricular fibrillation was recorded once; (*e*) slight prolongation of the P-R interval and (*f*) diminished QRS voltage. AUTHORS' SUMMARY.

THE "TRUE LUSCHKA DUCTS" AND THE "ROKITANSKY-ASCHOFF SINUSES" OF THE HUMAN GALL-BLADDER. BÉLA HALPERT, Bull. Johns Hopkins Hosp. **41**:77, 1927.

"True Luschka ducts" are duct-like structures found occasionally in the periphery of the wall of the gallbladder, occurring most frequently on the hepatic surface of the viscus and usually along the edges of the fossa vesicae felleae. They have a wall of their own with the histologic structure of intrahepatic bile ducts. The lumen is generally less than 0.3 mm. in diameter and is usually lined with a somewhat lower columnar epithelium than that of the gallbladder. Surrounding the lining epithelium there is a cellular connective-tissue layer rich in circularly arranged white connective-tissue fibers. "Rokitansky-Aschoff sinuses" are deeper outpouchings or sinuses of

the mucosa of the gallbladder, which dip down into the muscularis or extend as finger-like processes through the muscular coat into the perimuscular layer. The "Rokitansky-Aschoff sinuses" are identical with the structures which Rokitansky called "hernia-like outpouchings of the gallbladder mucosa" (1842), which Oschoff described as the "Luschka ducts" (1905) and which Shikinami later called (1908) the "Aschoff ducts," but they are not at all identical with the aberrant bile ducts which Luschka discovered (1863) in the wall of the human gallbladder, namely, the "true Luschka ducts." AUTHOR'S SUMMARY.

EXTRAMEDULLARY HEMATOPOIESIS IN ANEMIAS. DORSEY BRANNAN, Bull. Johns Hopkins Hosp. **41**:104, 1927.

Extramedullary hematopoiesis is a fairly common observation in certain types of anemia of infancy and childhood, and large tumor-like growths of hematopoietic tissue may occur, particularly in the hilum of the kidneys. The formation of blood outside the bone marrow is occasionally observed in the severe types of anemia in adults, even in the presence of a hyperplastic bone marrow. Hematopoiesis may be observed in the broad ligaments and in the organizing thrombi, as well as in the usual sites. Extramedullary blood production is to be regarded as a compensatory reaction. The production of blood may be observed in the broad ligaments and breasts of infants, under apparently normal conditions. In extramedullary hematopoiesis the process appears to start in foci of type cells, either erythropoiesis or leukopoiesis, which substantiates previous observations regarding formation of blood in the bone marrow.

AUTHOR'S SUMMARY.

THE RELATION OF THE PERITONEAL MESOTHELIAL CELLS TO THE PRODUCTION OF ASCITES. GEORGE HELLER, Bull. Johns Hopkins Hosp. **41**:207, 1927.

Neither the spleen nor the liver represents specialized areas for the transfer of fluids into the peritoneal cavity. The spleen does not become edematous by the collection of fluid in any of its tissues, except the layer of mesothelial cells. Fluids passing through the spleen and liver to the peritoneal cavity pass, at least in part, through the cytoplasm of the mesothelial cells.

AUTHOR'S SUMMARY.

CARCINOMA OF THE ISLANDS OF THE PANCREAS: HYPERINSULINISM AND HYPOGLYCEMIA. RUSSELL M. WILDER, FRANK N. ALLAN, M. H. POWER and H. E. ROBERTSON, J. A. M. A. **89**:348, 1927.

In a case of cancer originating in the islands of Langerhans, hourly doses of dextrose were required to prevent convulsions from spontaneous hypoglycemia. When the ingestion of the necessary sugar was delayed, the blood sugar fell below 0.03 per cent. The blood phosphates fell with the sugar and rose again on the restoration of the blood sugar. The liver functioned normally in deaminizing amino-acids and excreting bile and test dyes, but the glycogen stores proved abnormally stable to the action of epinephrine. Necropsy revealed a liver weighing 3,300 Gm. and containing 8.25 per cent of glycogen, carcinoma of the pancreas, and carcinomatous metastasis to the liver and lymph nodes. The cells of this cancer bore a striking resemblance to the cells of the islands of Langerhans, and alcoholic extracts made from the cancer tissue in the liver acted like insulin on injection into rabbits.

AUTHORS' SUMMARY.

ACUTE PANCREATITIS FOLLOWED BY DIABETES. LOUIS M. WARFIELD, J. A. M. A. **89**:654, 1927.

Four cases of acute pancreatitis followed by diabetes are described. One case was of the hemorrhagic form with fat necrosis. Two cases followed an attack of influenza.

NEPHROSES. J. B. MCELROY, J. A. M. A. **89**:940, 1927.

The term nephrosis, like many others in medical nomenclature, is not used in its etymologic sense, but having gained widespread use may well be retained to express the primary degenerative changes in the kidneys which these organs suffer by reason of their function as excretory organs. The acceptance of Fahr's classification would do much to satisfy the pathologic and clinical facts and to clarify the present confusion with reference to the subject. Lipoid nephrosis, though rare, occurs as a disease *sui generis*, without the presence of inflammatory lesions in the kidney.

AUTHOR'S SUMMARY.

STUDIES IN EXPERIMENTAL EXTRACORPOREAL THROMBOSIS. LEONARD G. ROWNTREE and TAKUJI SHIONOYA, J. Exper. Med. **46**:7, 1927. TAKUJI SHIONOYA, ibid., pp. 13 and 19.

A method is described for studying thrombosis in an artificial circulatory loop. In this way thrombosis formation under various conditions may be observed. The deposition of fibrin and of white thrombi may be independent processes.

EFFECT OF DIETARY PROTEIN ON REMAINING KIDNEY IN ADULT WHITE RATS AFTER UNILATERAL NEPHRECTOMY. THEODORE S. MOISE and ARTHUR H. SMITH, J. Exper. Med. **46**:27, 1927.

In animals on a high protein diet (85 per cent casein), glomerular and tubular lesions developed after nephrectomy, but no such lesions developed in animals on a standard ration (18 per cent casein). Young animals appear to have greater powers of adaptation to high protein rations than older rats.

ENLARGEMENT OF ADRENAL CORTEX IN EXPERIMENTAL UREMIA IN WHITE RATS. E. M. and L. L. MACKAY, J. Exper. Med. **46**:429, 1927.

Uremia was produced by removing both kidneys. Hypertrophy of the suprarenal cortex followed.

THE RHYTHMIC RANGE OF THE WHITE BLOOD CELLS IN HUMAN, PATHOLOGICAL LEUCOPENIC AND LEUCOCYTIC STATES, WITH A STUDY OF THIRTY-TWO HUMAN BONE MARROWS. CHARLES A. DOAN and LEON G. ZERFAS, J. Exper. Med. **46**:511, 1927.

In a study of twenty clinical cases with a wide range of diagnoses, repeated total counts of the white cells at intervals of fifteen minutes reveal a large fluctuation at various levels comparable to that found for the normal (1, 2). The granulocytes seem to follow a more or less hourly rhythm, the most marked shifting to the left in the Arneth pattern and the moment of greatest percentage of motility coinciding with the peaks. The independence existing between the peripheral blood concentrations of individual strains of white cells and the red cells, as determined by total and differential counts, their differential response to pathologic and pharmacologic stimuli, and their normal relative relations, all indicate some separate physiologic mechanism of control for each type of cell, either working through, or independently of, their sources of origin. The many factors to which the circulation of the blood, as such, is subject, the complexity of the influences on origin, maturation, delivery, longevity and destruction of each cell group and the limitations inherent in the present involved, indirect technics of counting combine to make any single observation subject to grave misinterpretation. The value to the clinician must come in repeated observations, at times when the diagnosis or a therapeutic procedure is in doubt, at frequent intervals, at other times over longer or shorter periods, but always with the relation between consecutive counts, rather than the absolute values, the important point for consideration. Both

the red and the white cells probably change their relative concentrations in the peripheral blood from time to time over a considerable range that is within normal physiologic limits, so that, in theoretical considerations and in practical functional estimations, a zonal concept with adequate individual extremes should always be kept in mind for both physiologic and pathologic states. A cytologic analysis of thirty-two bone marrows from human biopsy and autopsy material shows the striking reciprocity between the myelocytes and the mature polymorphonuclear leukocytes. This, together with the observed focal uniformity of maturation found in bone marrow, and the periodicity of the fluctuations of the neutrophils in the peripheral blood, leads to the formulation of the hypothesis of a constant functional withdrawal of granulocytes from the peripheral blood with a periodic delivery of new cells from the marrow, which in leukopenia and in leukocytosis represents a depression or a stimulation, respectively, of the normal mechanism. The nature and degree of the response are an approximate index of the cellular factor in the complex of the "resistance" of the particular individual.

AUTHORS' SUMMARY.

A STUDY OF THE PERIVASCULAR TISSUES OF THE CENTRAL NERVOUS SYSTEM, WITH THE SUPRAVITAL TECHNIQUE. LAWRENCE S. KUBIE, J. Exper. Med. **46**:615, 1927.

By means of the supravital technic, it has been found that the perivascular tissues of the brain contain normally two types of cells — lymphocytes and clasmatocytes. It is believed that these cells are always present and proliferate in situ, under both normal and pathologic conditions.

AUTHOR'S SUMMARY.

THE RELATION OF MONOCYTES AND CLASMATOCYTES TO EARLY INFECTION IN RABBITS WITH BOVINE TUBERCLE BACILLI. FLORENCE R. SABIN and CHARLES A. DOAN, J. Exper. Med. **46**:627, 1927.

The early reaction to intravenous tuberculous infection in the various organs of the rabbit reveals a pathognomonic response in the lungs within twenty-four hours; the specific response in the liver, spleen, lymph glands and bone marrow follows from the sixth to the fourteenth day. The development and extent of the pathologic process have been analyzed in terms of the activity of the monocytes and clasmatocytes. The criteria for differentiating these mononuclear phagocytic cells into two strains have been analyzed and the technics discussed. The clasmatocyte phagocytizes tubercle bacilli freely and fragments them, as it does all cellular and other débris. The monocyte stimulated to metamorphose into the typical epithelioid and giant cell of the Langhans type retains the tubercle bacilli intact, with power to survive and multiply, over long periods of time. The normal number of monocytes or the degree to which monoblasts may be stimulated to development and maturation, together with the activity of the clasmatocytes in destroying bacilli, in any particular region, would appear to be a function of the rapidity and extent of the local tubercular involvement.

AUTHORS' SUMMARY.

THE BIOLOGICAL REACTIONS IN RABBITS TO THE PROTEIN AND PHOSPHATIDE FRACTIONS FROM THE CHEMICAL ANALYSIS OF HUMAN TUBERCLE BACILLI. FLORENCE R. SABIN and CHARLES A. DOAN, J. Exper. Med. **46**:645, 1927.

The clasmatocyte, the cell with the power of fragmenting tubercle bacilli, the cell making the lesion of the so-called interstitial pneumonia, has been shown to be the overwhelming response to the special protein fractions, 304 and 903. Multiple hemorrhages, high fever and toxicity have marked the use of these fractions in every instance. The epithelioid and the giant cell of the Langhans type, making typical tuberculous tissue, have been the massive and

specific response of the peritoneal cavity to intraperitoneal injections of the phosphatide fractions, A-3 and A-4. These fractions have been entirely nontoxic in the dosages used.

AUTHORS' SUMMARY.

SECONDARY CARCINOMA IMPLANTED ON THE ENDOCARDIUM OF THE RIGHT VENTRICLE. ALBERT G. NICHOLLS, Canad. M. A. J. **17**:798, 1927.

When secondary malignant masses are found within the ventricles of the heart, they may be attached to the endocardium by implantation and incarceration, much as a tree grows out of the crannies of a rock when the wind has carried the seed to the spot; they may be free within the cavity, on the analogy of the ball or polypoid thrombus, or they may develop in the musculature and eventually encroach on the cavity. It seems certain, from the size and microscopic structure of the intracardiac mass in the first case at least, that a relatively small cancerous embolus had lodged in the lacunae of the ventricular wall and had subsequently grown into the considerable mass that was found.

AUTHOR'S SUMMARY.

CONGENITAL ATRESIA OF THE ALIMENTARY TRACT. W. P. H. SHELDON, Arch. Dis. Childhood **1**:279, 1926.

In 6,000 autopsies at the Great Ormond Street Hospital since 1900, there were twenty-eight cases of congenital atresia of the alimentary tract. Congenital narrowing without obliteration was found in six cases. The sites of obstruction were as follows:

	Atresia	Partial Stenosis
Esophagus	6	2
Duodenum		
Above biliary papilla	2	1
At biliary papilla	2	1
Below biliary papilla	2	0
Small intestine	13	0
Large intestine	3	2

ABNORMAL MATERIAL IN THE BRAINS OF RABBITS. CYRIL POLSON, Brit. J. Exper. Path. **8**:205, 1927.

A "mucinoid" material has been found in the brains of apparently healthy rabbits as well as in rabbits used in experiments.

HEREDITARY DEFORMITY OF FINGERS. N. CHILTON, Brit. M. J. **2**:15, 1927.

The middle and terminal phalanges were shortened. The body of each finger-nail was double, the two parts being separated by almost normal skin, which ran distally over the dorsum of the terminal phalanx and was continuous with the skin covering the tip of the finger. On both sides of this median strip of skin, nail tissue appeared, of the normal texture and elasticity. The cuticle was present on each side and overlapped the nails in the usual fashion. The intermediate central part was harder than normal skin and was longitudinally striated; it was, however, distinct from the nails. At the distal end there was the usual shallow transverse groove, where the free end of the nail should be. The little finger of the left hand approached the nearest to normal. A grandfather, the father, the brother, the sister and a niece exhibited the same deformity.

ON THE INVOLUTION OF THE UTERUS POSTPARTUM. J. TEACHER, J. Obst. & Gync. Brit. Emp. **34**:1, 1927.

Teacher's observations are based on studies of the uterus obtained at postmortem examination and on curetted material, the histologic observations and

the period elapsed postpartum being correlated. He found that involution progresses despite local or constitutional disease but is delayed by retention of the products of conception. By the first week there is a demarcation of the tissue to be shed off into the lochia, and by the second week the process of cleansing and shedding has progressed rapidly. A provisional mucous membrane is normally completed by the fourteenth day. The healing is comparable to that by granulation in the presence of sloughs and micro-organisms. The fourteenth day is regarded as the turning point at which building up exceeds retrogression. Though the healing process is far from complete at the end of three weeks, in from five to six weeks the involution is fairly complete. The evidences of recent pregnancy are given by organizing thrombosis and by the presence of pigmented phagocytes and the remains of uteroplacental vessels as hyaline masses.

A. J. KOBAK.

THE DISTRIBUTION AND SIGNIFICANCE OF ECTOPIC DECIDUAL CELLS. WILFRED SHAW, J. Obst. & Gynec. Brit. Emp. **34**:28, 1927.

Decidual cells can be found widely distributed in normal uterine pregnancies. They have been detected subserously in the uterus, in the subperitoneal tissue, in the omentum, in the pelvic lymph nodes and in the uterus, by the author and others. Independent of pregnancy they are found during the premenstrual phase in the cortex of the ovary as well as in the endometrium. The circulating hormone from the corpus luteum is a factor in their formation, and the decidual reaction is inherent with certain cells derived from the subcelomic mesoblast.

A. J. KOBAK.

COMPLETE ABSENCE OF GALL BLADDER AND EXTRAHEPATIC BILE DUCTS. NORMAN H. HILL, Lancet **2**:654, 1927.

A girl, aged 4 months, who had been jaundiced from the fourth day after birth, passed a considerable amount of blood from the bowels and stomach shortly before death. The liver was large and granular. There was no trace of the gallbladder or the extrahepatic bile ducts. Microscopically, "the liver showed an extensive cirrhosis mainly in the portal areas in which bile ducts were numerous." Some of the bile ducts were distended with bile.

THE DISTRIBUTION OF LYMPHATICS DEFINED BY FATTY ACID COMPOUNDS DEVELOPED IN THE AUTOLYSIS OF THEIR CONTENTS. J. L. SMITH and T. RETTIE, Proc. Roy. Soc. Med. **102B**:102, 1927.

The lipids contained in the lymphatics of the liver undergo postmortem autolysis earlier than those contained elsewhere in that tissue. Doubly refractive globules of "soap" may be formed in such quantity that the lumina of the lymph channels become filled continuously, revealing their anatomic form and arrangement.

ARTHUR LOCKE.

AMYLOID GOITER. CHARLES OBERLING, Ann. d'anat. path. **4**:125, 1927.

An involvement of the thyroid gland by amyloid in instances in which there is a general amyloidosis is of frequent occurrence. Amyloid infiltration of the thyroid as a primary lesion is apparently extremely rare, since Oberling found only three cases in the literature. He reports a fourth case in which amyloid was present in this gland only. The thyroid in this case was voluminous, being divided into two communicating parts, regular in outline and hard in consistency. There was a slight exopthalmos, but no other signs of exophthalmic goiter. The trachea was compressed. A diagnosis of a malignant goiter was made. The patient died following operation. Necropsy showed the symptoms of a chronic interstitial pneumonia in the lungs, bronchiectasis and a diffuse purulent bronchitis. The thyroid showed an unusual development of

the interstitial tissue which displayed all the characteristics of an amyloid substance. Embedded in this were numerous fatty cells. The parenchyma was composed of small irregular alveoli, widely separated from each other. The capsule was not unusual, and the lobulation of the gland was preserved.

The etiology of the localized amyloid infiltration is similar to that of a general amyloidosis. Two factors play a rôle in the genesis of this condition; a general and a local. The latter or the tissue agent is apparently connected with changes in the epithelial cells, leading to modification in the secretory activity of the cells.

B. M. Fried.

The Rôle of the Excretory System in the Pathologic Anatomy of the Pancreas. P. Hickel and J. Nordmann, Ann. d'anat. path. **4**:225, 1927.

In an investigation of a large number of pancreases with inflammatory, degenerative and neoplastic changes, the authors noted a nondifferentiated proliferation of the cells of the excretory canals which plays apparently a rôle in the formation of tumor. In certain pathologic conditions the acinar cells proliferate and lead to a destruction of the normal structure of the gland. In the proliferated areas, the cells form acini without any tendency towards transformation into islands of Langerhans. In diabetes accompanied by histologic lesions of the pancreas the acini as well as the islands of Langerhans are involved. In such cases the acini do not transforma themselves into islands, although there is a tendency toward such a formation. Epithelial tumors, according to Hickel and Nordmann, originate from the acinar elements only.

B. M. Fried.

So-Called Colloid Cancers of the Breast. Sotero del Rio, Ann. d'anat. path. **4**:258, 1927.

Rio states that in the colloid cancers the mucus is secreted by the epithelial cell independently from any degeneration. The secretion is normally present in the mammary alveolus; in these tumors it is only more abundant. The connective tissue secretes mucus also owing apparently to the inversion of the cellular polarity.

B. M. Fried.

Splenic Mycosis, a Histologic Study. A. Nanta, Ann. d'anat. path. **4**:373, 1927.

In some cases of splenomegaly seen in North Africa, Nanta found a fungus in the spleen which he was able to cultivate and which he believes to be the cause of the splenic enlargement. The infection in these cases is confined to the corpuscles of Malpighi which become infiltrated with a ferruginous pigment and also sclerosed. These scleropigmentary nodules form mycotic tubercles. In addition to the fungus, cultures show also the presence of bacteria. It therefore seems difficult to elucidate the rôle of the fungus in enlargement of the spleen and also in the pathologic changes of the extrasplenic lesions which usually accompany the disease of the spleen. From the histology of the inflammatory lesion and also from the biologic properties of the "sterigmatocystis" (a term introduced by the author by which they designate the fungus) he is, however, inclined to the belief that splenic mycosis is a disease entity.

B. M. Fried.

Two Cases of Mycotic Aneurysm of the Heart with Destructive Lesions of the Auriculoventricular Bundle Without Bradycardia. Ivan Mahaim, Ann. d'anat. path. **4**:488, 1927.

The clinical syndrome of a complete auriculoventricular (A-V) dissociation was and is still attributed by most cardiologists to a destructive lesion

of the bundle of His. But more recent investigations have shown that a slow pulse due apparently to a complete A-V dissociation may occur in spite of the fact that the continuity of the bundle has not been entirely destroyed. Some observers were able to demonstrate a complete dissociation in the presence of a perfect histologic integrity of the pathway of conduction. In the presence of such facts one is inclined to attribute the A-V dissociation to functional disturbances.

Mahaim reports two cases of patients in whom the bundle of His showed on histologic examination complete phlegmonous destruction but whose pulse during life was regular, varying between 100 and 120 per minute. Mahaim quotes Vaquez and Mackenzie who attributed paroxysmal tachycardia to irritative lesions of the bundle of His and more particularly of that of Tawara. He wonders whether the inflammatory infiltration of the lower preserved parts of the bundle could lead to tachycardia in these two cases analogous to that noted by Mackenzie in paroxysmal tachycardia.

B. M. FRIED.

THE PATHOLOGIC ANATOMY OF MYCOTIC SPLENOMEGALY. P. EMILE-WEIL, R. GRÉGOIRE, and FLANDRIN, Ann. d'anat. path. **4**:587, 1927.

Nanta and Pinoy believe that in a number of instances the splenomegaly observed in North Africa is caused by a fungus which they have designated as *Sterigmatocystis nidulans*. By investigating sixteen splenomegalic patients, Emile-Weil and others found that the lesion described by Nanta was present in seven spleens; six were removed at operation and one was found at necropsy. They state that splenomegaly due to a mycosis is apparently frequent in Paris. Their report deals with the microscopic change in the lesion. The spleen is large, sometimes weighing from 2 to 2.5 Kg. in an adult. It is uniformly enlarged, smooth, hard and reddish, showing greatly enlarged splenic veins. On a cut surface small round or stellate nodules, from 2 to 3 mm. in diameter, are conspicuous. These are considered an essential trait of the lesion. Besides the nodules the organ shows sclerosis and infarcted areas due to arterial thrombi. The nodule, which, according to Weil, is as characteristic of this lesion as the tubercle is in tuberculosis, is found in the splenic pulp and is prominent. The center of the nodule contains a vessel with a thickened wall but without endo-arteritis. The vessel is surrounded by altered connective tissue, by fibroblasts and at the very periphery by multinucleated, giant cells which is indeed a typical histiocytic reaction. Hyaline masses and some yellowish pigment, which the authors could not interpret, are also present. The parasite is lodged within the connective tissue of the described nodule. It is conspicuous as a dense and voluminous mycelium stained blue and recognizable by its segments. Spores are also present. The mycelium is frequently disclosed in the middle arterial coat, thus destroying the mediums.

Changes found in the spleen outside of the nodule are not specific. The liver shows cirrhosis. Mycelium has not been found in this organ. The parasite is cultured acrobically on agar-ascitic fluid and also on Sabouraud's medium. The fungus develops within from eight to ten days following the inoculation. It is apparently *Aspergillus* but not of the fumigant variety.

B. M. FRIED.

A MIXED TUMOR OF THE UTERUS WITH METASTASES TO TIBIA. IVES DELAGENIÈRE and P. BEAUCHEF, Ann. d'anat. path. **4**:617, 1927.

A tumor of the uterus in a woman, aged 54, is reported. The growth was composed of cartilage, bone and of tissue having a gliomatous aspect. The metastases were composed of one type of sarcomatous tissue. The authors found reports of only eighteen other cases of mixed uterine tumors in the literature.

B. M. FRIED.

INDICANEMIA IN NEPHRITICS AND EXPERIMENTAL NEPHRITIS PRODUCED WITH INDOL. ALEXANDRE G. PHOCAS, Ann. de l'Inst. Pasteur **41**:576, 1927.

Small continued doses of indol can produce experimental nephritis in rabbits. The neutralization of indol by sulphur ions results in the formation of indican. In nephritic patients there may be an excess of indol which is not neutralized. The use of small daily doses of sodium sulphate is advised.

G. B. RHODES.

CONTRIBUTION TO THE KNOWLEDGE OF GRANULOMA OF THE TENDON SHEATH. A. MARIO, Tumori **1**:124, 1927.

The author describes a fibrous tumor of the common sheath of the peroneus muscles in a young girl, aged 24. In the central parts of the growth the tissue is more cellular and contains multinuclear giant cells. Mario believes that the condition is the result of a fibrous degeneration of the tendon sheath most likely due to a mechanical or chemical cause which has produced a simple hyperplasia. It seems more likely that the tumor is a slowly growing giant celled sarcoma.

W. OPHÜLS.

ACTION OF LIGHT RAYS ON LYMPHOID ORGANS. J. JOLLY, Le Sang **1**:1, 1927.

Jolly studied the lesions caused in lymphoid tissues by short wave rays other than roentgen or gamma rays. Changes produced by the ultraviolet rays have heretofore been noted only in the skin and accessible membranes such as the cornea and the lingual mucosa. Owing to absorption of the ultraviolet rays by the skin the lymphoid organs appeared unaffected by the rays. In his experiments, Jolly exposed the inguinal glands and the thymus of guinea-pigs and rabbits to rays, after having incised the corresponding part of the skin. Under ultraviolet rays, the lesions in the thymus were limited to the cortical portion of the gland directly exposed to the rays. Pyknosis and nuclear necrosis were present in the thymocytes. The connective tissue remained intact. In the inguinal glands, the lesions were analogous to those in the thymus. The glandular follicles, especially the germinal centers, were involved. The character of the lesions and the period of latency were the same as when roentgen rays were employed. In another set of experiments rats were injected with erythrosine, and then the thymus was exposed to sunlight. The animals were killed from twelve to twenty-four hours after the exposure. The lesions in the gland were the same as after exposure to ultraviolet rays. Changes in the thymus did not occur from exposure to sunlight without the previous injection or from injection without exposure to sunlight. Chemical changes in the body fluids, caused by the fluorescent substances, were responsible for the lesions. Evidently short wave rays exert, besides a direct action, also a toxic secondary action, the character of which is yet unknown.

R. LAPIDUS.

PATHOGENESIS OF ANGIOMA. P. EMILE-WEIL, Le Sang **1**:35, 1927.

Emile-Weil's experience includes fourteen cases of angioma. Ten of the patients were women. In eleven cases, the lesion was congenital. All forms of the disease were sporadic; none was familial. Seven of the patients presented a lesion of the liver associated with a hemorrhagic condition. In six, hemogenia coincided with changes in the capillaries. Hepatic and homogenic disturbances were absent in only one case, in a child, aged 3. This is explained by the fact that hemogenia usually develops at the time of puberty. There appears to be an analogy between hepatic diseases in which ruby-colored spots and enlarged capillaries develop in adults and Osler's disease, which is characterized by an hereditary hemorrhagic angiomatosis. Another analogy is found in congenital angioma. The conclusion is that angioma is not

merely a local lesion; its development is connected with hepatic insufficiency. The coexistence of changes in the blood and in the capillaries is the result of a pathologic process in the embryonal islands of Wolff and Pander. Capillary angiomas of the neck which occur frequently in the new-born, disappear spontaneously within the first year of life. In the other cases, hepatic and splenic extracts as well as subcutaneous injections of blood have been tried without success.

R. Lapidus.

Clinical and Experimental Studies of the Localized and Generalized Ostitis Fibrosa. F. Mandl, Arch. f. klin. Chir. **143**:245, 1926.

Tetany is frequently observed in persons with rickets and osteomalacia, diseases both of which are related to the function of the parathyroids. Ostitis fibrosa is often found following them. Hoffhein reported forty-five cases of enlarged parathyroid glands (parastruma), and in eighteen of these cases ostitis fibrosa, in eight osteomalacia and in two rickets were observed. Erdheim saw enlarged parathyroid glands in patients with paralysis agitans. After extirpation of these glands, impairment of healing of fractures and decalcification of teeth occurred. Erdheim interprets the parathyroid enlargement as compensatory hyperplasia, while other investigators feel that the differential diagnosis between adenoma and hyperplasia of the parathyroid gland is difficult or even sometimes impossible. Mandl describes a patient with generalized ostitis fibrosa which improved markedly after extirpation of the enlarged parathyroids. The urinary calcium decreased to one sixth of the previous amount and the patient, who had been unable to walk or stand, could stand and even walk with the aid of crutches after the operation. The pains decreased considerably, and the roentgenograms seemed to show a higher degree of calcification after the extirpation than before it. The result of this procedure seems to disprove Erdheim's theory of the function of the parathyroid gland. Robinson explains the decalcification of the bone as the result of a hypofunction of the parathyroid produced by the tumor, which impairs the normal secretion of the hormone. Therefore, an extirpation of the tumor would result in a reestablishment of the normal function. In localized ostitis fibrosa, enlarged parathyroid glands were seen only once. This disease is interpreted as the result of a multiple disturbance of the glands of internal secretion. Attempts to produce ostitis fibrosa in dogs by curettement of the spongiosa of the shaft of the femur were unsuccessful. This tends to disprove Lexer's theory of the traumatic origin of bone cysts. The subsequent injection of sodium iodide into the cysts after removal of the bone marrow by irrigation to prevent the clotting and organization of the blood did not result in the production of cysts. The traumatic destruction of bones in rats with experimental rickets did not cause bone cysts.

W. Hueper.

Cysts of the Pancreas. Heinrich Müller, Arch. f. klin. Chir. **143**:285, 1927.

There are reports of about 460 cases of pancreatic cysts on record. To this number, Müller adds two. They are classified from a clinical standpoint into traumatic and nontraumatic cysts. They are most frequent between the ages of 30 and 40, but have been observed in a child, aged 5 months, as well as in a person, aged 76. The frequency in the sexes is the same. Traumatic cysts are more frequent in men than in women (3:1 to 7:1). Traumatic cysts usually develop from three to five weeks after the trauma, but may be observed as long as eight years afterward. Nontraumatic cysts frequently follow inflammatory processes in the epigastrium, e. g., cholecystitis. In a series of 196 cases, 146 belonged to this group. They are more frequent in females than in males (52:32). Symptoms in both groups are the same: abdominal pains, loss of appetite, belching, vomiting, obstipation, loss of weight, jaundice, dyspnea and, rarely, diarrhea. The urine may contain indican. The diastase in the

blood may be increased. Hyperglycemia is rare as are fatty diarrhea and the presence of muscle fibers and starch in the stools. Increase in temperature and bronzing of the skin are sometimes observed. The cyst is usually found in the left epigastric region, sometimes going over the umbilical region into the pelvis. The cysts may vary greatly in size and are rarely movable. The content has a specific gravity of from 1.010 to 1.015, is alkaline, yellow or brownish or sanguinolent, contains albumin, mucus, sometimes soapy masses and bits of pancreatic tissue, and is of a watery or jelly-like consistence. It is usually sterile. The pancreatic ferments may be present or absent. In the differential diagnosis, almost all cystic formations in the abdominal cavity have to be considered. Pancreatic cysts are divided into: proliferative cysts (adenocystomas), retention cysts (due to obliteration of pancreatic duct, interstitial pancreatitis, etc.), degenerative cysts (caused by degeneration of solid tumors, extravasations, degenerations in chronic pancreatitis, etc.), pseudocysts (of an inflammatory or traumatic origin) and echinococcus cysts. True cysts usually have a thicker wall than pseudocysts. In twenty-four patients with true cysts, only seven had a cubical or cylindric epithelium. The location in the head is the more frequent. In seven cases, also, a carcinoma of the pancreas was present. A child, aged 5 months, had a congenital cyst. Echinococcus cysts of the pancreas represent 0.12 per cent of all echinococcus cysts and 6.5 per cent of all pancreatic cysts. Forty-two cases are reported. Eosinophilia of the blood and the complement-fixation test are important for the diagnosis.

W. HUEPER.

SACROCOCCYGEAL CHORDOMA. RUDOLPH ANDLER, Arch. f. klin. Chir. **143**:467, 1927.

Chordomas originate from remnants of the fetal chorda dorsalis. They occur at the cranial as well as the caudal part of the spinal column. Thirty-three cases of sacrococcygeal chordomas are recorded. From a capsule of connective tissue septums project into the tumor, producing on cross-sections an alveolar structure. The tumor tissue is gray or brown and is transparent, jelly-like or bacon-like. Due to frequent necroses, cystic formations may cause a honeycomb-like appearance. Hemorrhages and calcifications occur. Two types of tumor cells are found. In the periphery of the cell nests, oval shaped or polygonal solid cells with larger nuclei and granulated cytoplasm are present. They represent young immature cells. The cells of the second type are large cells the shape of a signet ring, containing a large vacuole (physaliphores). The content of the vacuole is composed of mucus and glycogen. The nuclei are distinctly stained. The matrix is amorphous, hyaline with granulations and striations and is chemically composed of mucus. The occurrence of glycogen is disputed. The distribution and the ratio of chordoma cells and intercellular substance varies. The cells originate from the ectoblast and sometimes have a sarcomatous or carcinomatous structure. The stroma is vascular and may show perivascular round cell infiltrations. In malignant chordomas more immature cells, syncytial cells and atypical mitoses are observed. Invasion of veins, lymphatics and muscle tissue is then present. Metastases are rare. Trauma as a contributory factor is recorded in 18 per cent. The tumor was observed in twenty-four males and nine females between 22 and 68 years of age. The symptoms will depend on the direction of growth and the location of the tumor. There is a central type (in the os sacrum) and a peripheral and enteric (primary in the wall of the sigmoid) type. Symptoms are: swelling in the sacrococcygeal region causing a mechanical obstacle in sitting and lying down, the feeling of carrying a foreign body, but no pains on palpation if the tumor is not located in the sacral canal. With the extension of the tumor, there may be pain in the region of the sacral and coccygeal nerves, paresis of the nerves, intestinal obstruction and disturbances of the bladder and rectum. There may be painless intervals. Palpation reveals soft and firm regions. Roentgenograms show destruction of bone. The rapidity of growth varies considerably (from four to ten months to eight to eighteen years). Prognosis is unfavorable on

account of frequent recurrences after removal and the dangerous complications which may arise before and after operation. The differential diagnosis involves sarcoma, enchondroma, carcinoma, syphilis and tuberculosis.

W. HUEPER.

CELLULAR MORPHOLOGY OF THE KIDNEY IN RELATION TO FUNCTION. T. KOSUGI, Beitr. z. path. Anat. u. z. allg. Pathol. **77**:1, 1927.

In four subdivisions under the general heading, "Beiträge zur Morphologie der Nierenfunktion," Kosugi reports the results of work carried out under the direction of Aschoff, in which morphologic changes in the tubular epithelium of the rat's kidney are correlated with function. The first subdivision is entitled "Granuloid" and gives the description of a structural peculiarity of the epithelium which the author claims has escaped attention. In material which has been fixed in sublimate-containing fluids and stained by Heidenhain's iron hematoxylin or the Altmann-Schridde granule methods, the rods or mitochondria and the brush border are perfectly preserved, the morphologic picture being that with which all are familiar. If the same staining methods are applied to material fixed in Orth's fluid, there is intensely stained, in the supranuclear portion of the cell, a structureless material, apparently of viscid consistency, which is not preserved by other fixing methods. This material retains the iron hematoxylin stain more tenaciously than any other cellular element. It is distinct from the cytoplasmic rods and is covered superficially by the brush border of the cell. It increases in amount as the cell enlarges and finally, when the swollen portion of two or more adjacent cells have come in contact, the material is emptied into the lumen of the tubule through the brush border, which is not, however, lost in the process and is a highly differentiated element of the cell. This material, which Kosugi has termed "granuloid," is least prominent in the proximal portion of the convoluted tubule and becomes progressively greater in amount distally, often completely hiding all other cell structures in the transitional piece of the tubule. On morphologic grounds, Kosugi concludes that the epithelium of the convoluted tubules absorbs the dilute glomerular filtrate, the cells becoming finely vacuolated during the process. Within the cells the substances to be excreted are concentrated and become visible as the material which he has termed granuloid, and which is emptied into the lumen after concentration. The fluid material together with those substances which are to be retained are returned to the blood and lymph stream by means of the basal rods or mitochondrial apparatus. The immediate morphologic effects of diuresis, brought about by injection of salt solution or of urea or by ligation of one ureter or removal of one kidney, the latter two of which procedures throw the entire function of both kidneys on one organ, are described in a second subdivision. The convoluted tubular epithelium becomes markedly vacuolated and the concentrating capacity of the epithelium is interfered with, as is evidenced by the failure of formation of granuloid material. In the kidney in which the ureter is ligated, dilatation of tubules occurs in two stages and is accompanied by absence of granuloid in the tubular epithelium. The first stage, which is the result of stagnation of secreted urine, sets in immediately after ligation, lasts about twenty-four hours, and involves the portion of the tubules distal to the thin limb of Henle's loop. The second stage of the dilatation is due to a backflow of urine from the filled pelvis, occurs in those tubules which take a perpendicular course through the papilla, and involves the entire tubule to Bowmann's capsule. In the third subdivision, the effects of sublimate poisoning on the kidney of the rat are described. The sublimate is excreted in the glomerular filtrate in a concentration that has little effect. It is resorbed by the convoluted tubular epithelium, in which it is concentrated together with the other substances in the filrate, causing damage to and destruction of specific cells when the concentration becomes great enough. With large losses diffuse necrosis of the cortex occurs, but the widespread necrosis is secondary to the destruction of the convoluted tubular cells.

In the hydronephrotic kidney the characteristic changes are produced if the epithelium still retains sufficient function to concentrate the glomerular filtrate. Section of the nerves of the blood vessels of the kidney does not alter the specific effect of sublimate poisoning, disproving the neuropathic theory of Ricker. The final portion of Kosugi's contribution relates to the changes caused by vinylamine. The characteristic necrosis of the epithelium of the straight tubules, caused by this substance, has been explained by Oka as the result of concentration in that portion of the tubular system in which absorption of water occurs, by Levaditi as the result of a specific affinity of the straight tubular epithelium for the poison, and by Ricker on the basis of his neurovascular theory. Kosugi finds that the localization of the changes in the medulla, usually described as characteristic for vinylamine, is due to admixture of other substances. If pure vinylamine is used in adequate dosage, the substance is excreted in the glomerular filtrate and is concentrated in the proximal convoluted tubule, where it produces its first damaging effect. The medullary localization of the changes which usually follow the use of the material are due to the fact that from the impure material usually used pure vinylamine is slowly formed in such low concentration that it has no effect on the glomeruli or concentrating epithelium. It reaches a concentration high enough to cause damage only in the straight tubules, in which the final absorption of water alone occurs.

O. T. Schultz.

Reactivation of Latent Tuberculosis and Its Causes. A. Arnstein, Beitr. z. klin. d. Tuberk. **65**:713, 1927.

In order to determine the frequency of the various causes for the reactivation of pulmonary tuberculosis, the data of 800 consecutive autopsies were analyzed. Three large groups were distinguished: 1. Patients who died of chronic tuberculosis, or who showed, besides some other disease, an extensive chronic tuberculosis. 2. Patients who had, besides their lethal diseases, small foci of fresh and active tuberculosis (these are the cases of special interest for the present study). 3. Cases in which active tuberculosis was not found. There were 176 cases in group 2. The frequency of extensive tuberculosis decreased with increasing age, while the frequency of fresh and small foci of active tuberculosis increased with increasing age. In grouping the cases belonging to group 2, according to the cause of death, it was found that in 52 per cent of the cases of arteriosclerosis, fresh tuberculous foci were found. The order of frequency follows: chronic valvular diseases, mesa-aortitis, emphysema, pneumonia and pleuritis, malignant tumors, pericarditis and endocarditis. Freshly active foci were found much less frequently in the presence of an acute fatal disease.

Max Pinner.

Fibrocaseous Tuberculosis of the Lymph Glands. H. Mayser, Beitr. z. klin. d. Tuberk. **66**:284, 1927.

Two cases of fibrocaseous tuberculosis of the lymph glands were reported, one of which showed localized tumor-like processes in the mesenteric and paraaortal lymph nodes with hyaline and caseous necrosis. The other case showed generalized lymphoid hyperplasia. In both cases, the terminal disease was miliary tuberculosis.

Max Pinner.

Genital Tuberculosis in the Female; Primary Tuberculosis of the Fallopian Tubes. H. H. Kalbfleisch, Beitr. z. klin. d. Tuberk. **66**:328, 1927.

The case of a girl, aged 17, is reported, who was admitted to the clinic with the symptoms of peritonitis. Laparotomy showed an extensive fibropurulent generalized peritonitis. The patient died one day after the operation. The

history indicated that several weeks before death, attempts at artificial abortion were done; the postmortem examination revealed tuberculosis of the genital organs and generalized miliary tuberculosis. By exclusion, the seat of the primary focus was considered to be in the tubes. The infection occurred most probably at the attempt at abortion. The further propagation was chiefly hematogenous and did not reveal any evidence for a descending process.

MAX PINNER.

THE PATHOGENESIS OF PULMONARY HEMORRHAGE IN TUBERCULOSIS. W. PAGEL, Beitr. z. klin. d. Tuberk. **66**:631, 1927.

In cirrhotic tuberculous pulmonary tissue, alterations of small blood vessels are found which are of varicose nature. Such varicose vessels are frequently seen on the inner surface of dilated alveoli and bronchioli. Similar changes are found in productive tuberculous processes which are not as yet cirrhotic. The rupture of such dilated vessels is considered a frequent cause of pulmonary hemorrhage.

MAX PINNER.

PARAFOCAL CAVITIES IN PULMONARY TUBERCULOSIS. W. PAGEL, Beitr. z. klin. d. Tuberk. **66**:545, 1927.

Next to tuberculous foci, particularly primary foci, and Puhl's foci of reinfection, formations of small cavities are sometimes observed which are here designated as "parafocal." They represent either simple emphysematous blebs, or circumscribed bronchiectatic emphysema. The tuberculous processes may extend into the wall of such cavities, especially if the first focus shows exacerbation. Similar pictures are sometimes found in primary cavities. Tuberculous alterations in parafocal cavitations may be the result of the expulsion of the caseous center in one of two foci, situated closely together.

MAX PINNER.

HISTOLOGIC ALTERATIONS IN THE SPLEEN IN CHRONIC PULMONARY TUBERCULOSIS. T. PETROFF, Beitr. z. klin. d. Tuberk. **66**:660, 1927.

The most important change in the histologic structure of the spleen in tuberculosis is a predominance of the reticulo-endothelial cells and of the reticular stroma, which is frequently thickened. The reticulo-endothelial cells are hypertrophied and actively phagocytic. Since mitoses are not frequent in them, the predominance of the cells is explained by a relative decrease of other cell types, particularly small lymphocytes. The lymphocytes show frequently necrobiotic processes. Plasma cells are numerous. The fat content is decreased; the blood pigment is increased.

MAX PINNER.

TRACHEOPATHIA CHONDRO-OSTEOPLASTICA. P. KIMMELSTIEL, Centralbl. f. allg. Path. u. path. Anat. **39**:469, 1927.

The author summarizes results already published in his "Doktordissertation," Hamburg, 1925. The appearance of cartilage and bone islands in the tracheal mucosa is related to preceding fatty changes. Both bone and cartilage occur in all cases, but one or the other may predominate in individual islands. The new growths occur between the tracheal rings, never in the pars membranacea, and when they lie in contact with the tracheal rings they present a definite fatty-elastic demarcation.

GEORGE RUKSTINAT.

THROMBOLYMPHANGITIS OF THE THORACIC DUCT. H. WURM, Centralbl. f. allg. Path. u. path. Anat. **39**:545, 1927.

A man, aged 44, entered the hospital with cardiac decompensation, dyspnea, fever, cough production of bloody sputum, and anasarca; four days later, he

developed edema of the left side of the face and left arm and died two days later. At the autopsy were found: an endolymphangitis of the end of the thoracic duct; an obturating thrombus at the junction of the left internal jugular and subclavian veins with peripheral prolongations 2 cm. long; extensive infected infarcts of the left lung, and a fibrinohemorrhagic pleuritis in the left lung, from which 1,000 cc. of pus was drained. The explanation of the course of events is this: Because of cardiac incompetence the patient developed pulmonary thrombi which led to lung infarcts, and these then became infected with low grade streptococci. The latter gained access to the thoracic duct through either the left ductus bronchomediastinalis or the ductus thoracicus from the left pleura. Because of the sluggish circulation the duct wall first became inflamed (as proved by more advanced organization of the mural clot) and from here the infection spread to the neighboring veins. The valves of the heart did not show any lesions.

GEORGE RUKSTINAT.

PERICARDIAL DIVERTICULA. G. G. NEPRJACHIN, Centralbl. f. allg. Path. u. path. Anat. **39**:548, 1927.

In the body of a man, aged 52, who had died from pulmonary tuberculosis, Neprjachin found a diverticulum 6 cm. long, 1.5 cm. in diameter at its proximal end and 1.8 cm. at its distal end, connecting by a pencil-sized opening with the pericardial cavity near the right auricle. Its lining and wall were identical with those of the pericardial sac and were free from all inflammation. This diverticulum is of the true congenital variety, of which only three others are reported.

A review of the literature reveals in addition, reports of fifteen diverticula resulting from pathologic processes and divisible into three types. Pulsion diverticula have thin walls and result from a rupture of the fibrous layers and a herniation of the serous membrane, usually in connection with hydropericardium and cardiac hypertrophy. Such diverticula may be multiple and range from those the size of a pea to those the size of a fist. Traction types result from adhesions to adjacent organs such as the lung and diaphragm. Cystic types are connected to the pericardium by narrow stalks, and at least one such has been proved to be of syphilitic origin.

GEORGE RUKSTINAT.

MULTIPLE AND DIFFUSE ENDOTHELIOMA OF THE MENINGES. J. CASPER, Deutsche Ztschr. f. Nervenh. **96**:85, 1927.

Several cases of multiple endothelioma are reported in detail with a discussion of their origin. Casper believes Cushing's term meningioma best for these tumors.

ROY GRINKER.

A CASE OF DURAL ENDOTHELIOMA OF THE CORTEX WITH AN UNUSUAL COMPLICATION. A. GROENEVELD and G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **97**:32, 1927.

A dural endothelioma over the left hemisphere caused marked edema on that side with distortion of the ventricular system. The opposite cerebral peduncle was pressed against the midbrain by the wall of the tentorium and the base of the skull.

ROY GRINKER.

TUMORS OF THE BRAIN WITH POLYMORPHONUCLEAR LEUKOCYTOSIS OF THE SPINAL FLUID. W. SCHARPFF, Deutsche Ztschr. f. Nervenh. **96**:112, 1927.

A glioma of the corpus collosum caused a large leukocytic meningeal infiltration which the author attributed to the toxic action of the tumor.

ROY GRINKER.

EXAMINATION OF THE CIRCULATION OF CEREBROSPINAL FLUID WITH HELP OF INTRAVENOUS INJECTIONS OF FLUORESCEIN. G. SCHALTENBRAND and T. PUTNAM, Deutsche Ztschr. f. Nervenh. **96**:123, 1927.

Intravenous injections of fluorescein result in a passage of the drug through the vessels of the choroid plexus and to a less extent through the vessels of the subarachnoid space into the cerebrospinal fluid. The authors conclude that this speaks for the transudation theory of the formation of liquor. The animal studied did not have any foramen of Magendie; the foramina of Luschka only were present.

ROY GRINKER.

THE ANATOMIC BASIS OF VEGETATIVE DISTURBANCE IN MENTAL DISEASES. A. STIEF, Deutsche Ztschr. f. Nervenh. **97**:112, 1927.

Severe changes were found in the diencephalon in general paralysis. In the same areas, patients with senile dementia revealed atrophic and senile placques. The author explains the cachexia and the subnormal and high body temperatures by the localization of lesions in the diencephalon.

ROY GRINKER.

MUCOID DEGENERATION OF THE OLIGODENDROGLIA. P. BAILEY and G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **97**:231, 1927.

In a case of encephalitis periaxialis diffusa (Schilder's disease), the authors found the mucoid degeneration of oligodendroglia, which Grynfeltt first described to be identical with Penfield's acute swelling of the oligodendroglia. The article contains the best illustrations of this type of change yet published.

ROY GRINKER.

RELATION OF ACANTHOSIS NIGRICANS TO OTHER LESIONS OF THE SKIN. H. HAMDI and T. HALIL, Virchows Arch. f. path. Anat. **263**:412, 1927.

In addition to the basal cell layer, the glands of the skin and their ducts are found to have undergone growth. The condition is frequently associated with cancer, and the authors suggest an association with other abnormalities of the skin, since in one of their cases a dermoid was present and in the other an overgrowth of cutaneous glands was seen.

BENSON BLOOM.

HISTIOGENESIS OF GIANT-CELL EPULIS. A. W. RYWKIND, Virchows Arch. f. path. Anat. **263**:415, 1927.

The giant-cell epulis is thought to represent a type of granulation tissue arising from the deep intra-alveolar parts of the paradentium. Histologically, the tumor develops first as a simple granuloma, then as an angiogranuloma and finally, through the formation of giant cells from the endothelium of the blood vessels, into the giant-cell type. The giant-cells, instead of degenerating, give rise to fibroblasts, and the various stages of this transformation result in the polymorphous character of the cells. Epulis is considered to be a localized form of ostitis fibrosa, its peculiarities being due to local anatomic and physiologic conditions.

BENSON BLOOM.

MICROSCOPIC CHANGES AND PATHOGENESIS OF ARTHRITIS DEFORMANS. G. POMMER, Virchows Arch. f. path. Anat. **263**:434, 1927.

In a long polemic, directed in great detail against those who have refused to accept as characteristic his observations on the microscopic changes of arthritis deformans or to agree with his views of the functional origin of the disease, Pommer reiterates his previous conclusions on the microscopic changes and the interpretations drawn therefrom. According to Pommer, the formation of the hypertrophic marginal ridges and ledges of the joints, which are

produced by proliferative changes in the subchondral osseous layer and which consist of newly formed bony trabeculae separated by fibrous tissue, is characteristic of the disease. A moderate amount of bone resorption also occurs. The bone trabeculae grow upward, toward and into the covering cartilage, which shows a variety of changes, the most important of which are localized areas of resorption and pressure atrophy. Associated with these regressive changes are calcification and fibrillation of the cartilage and ingrowth of newly formed blood vessels and connective tissue. Of greatest interest for Pommer is the fact that even without the formation of macroscopically visible ridges or ledges, the characteristic microscopic changes may already be present beneath a partly eroded cartilage. The second portion of the article is directed chiefly against J. Heine, who does not agree with Pommer in the latter's conception of the mechanical and functional origin of the disease. Most important in the production of the changes in the joints is prolonged pressure, which because of the nature of the occupation or the position of the joint, is applied at the margin of a mobile joint. This causes, first, abnormality in the elasticity and fibrillation of the cartilage, followed in turn by pressure atrophy, subjecting the underlying bone to trauma as the result of which there develop the characteristic subchondral changes, which are interpreted as a chronic, nonexudative, productive inflammatory process. A third section, devoted to the misplaced islands of cartilage found in the bone beneath the true joint cartilage, is also directed chiefly against Heine, who had explained the islands as direct downgrowths of the surface cartilage. According to Pommer, they arise chiefly from viable cartilage cells transported by the local lymph and blood vessels as the result of the mechanical disturbances to which the joint cartilage is subjected.

O. T. Schultz.

Water and Lipoid Content of Suprarenals. A. Materna and E. Januschke, Virchows Arch. f. path. Anat. **263**:537, 1927.

In analyses of suprarenals from various types of disease, certain fairly definite relationships were found. The sum of lipoid and water content, expressed in percentage of total weight, was constant, but the lipoid and water content were inversely related to each other. For example, in circulatory disturbances, lipoids were high and water low. In acute infectious diseases, the converse was true. In general, the more acute the death the lower the weight of the suprarenals. An increase in weight was mostly due to water. Analyses were also made of the suprarenals of guinea-pigs in various conditions, including hunger, pregnancy, chloroform poisoning, and acute and chronic infections. In these, too, the variations of lipoid and water content were constant for the individual conditions present.

Benson Bloom.

Free Fibrin Bodies of Pleural Cavity. M. Brandt, Virchows Arch. f. path. Anat. **263**:574, 1927.

Free fibrin bodies have been reported following artificial pneumothorax. By injecting oil of tar into the pleural cavity of dogs, such bodies, free and adherent to the lung, were produced.

Benson Bloom.

Hypoplasia of the Pancreas. B. Kriss, Virchows Arch. f. path. Anat. **263**:591, 1927.

According to Kriss, complete aplasia of the pancreas has been seen only in monstrosities, and only four cases of hypoplasia of this organ are recorded in the literature. He adds two cases, one in a woman, aged 62, in whom the tail and body of the pancreas were absent, and the other in a boy, aged 53 days, in whom the pancreas was represented by a mass the size of a hazelnut attached to the duodenum. In neither case had sugar been detected in the urine.

O. T. Schultz.

CONGENITAL DEFECT OF THE DIAPHRAGM. P. CARTELLIERI, Virchows Arch. f. path. Anat. **263**:599, 1927.

Nine examples of defect of the diaphragm in fetuses and new-born infants are described in detail. In seven, the diaphragm was defective on the left side, in one on the right side, and in one there was left sided herniation without defect. In two cases, absence of the greater portion of the left side of the diaphragm was associated with herniation of the right side. Although Beneke's conception that excessive growth energy of the abdominal organs as compared with those of the thorax is a factor in the genesis of diaphragmatic defect is accepted as plausible, the author does not believe that his cases offer evident support of this theory. Jahn's theory that the primary condition may be a disturbance of growth of the pleuroperitoneal fold is held to be more probable.

O. T. SCHULTZ.

BILOCULAR URINARY BLADDER. R. CHWALLA, Virchows Arch. f. path. Anat. **263**:632, 1927.

In a human fetus 32.5 mm. long, at which stage the ureteral membrane should have disappeared, the membrane had persisted on one side and by transposition toward the midline had caused the formation of an accessory bladder cavity.

O. T. SCHULTZ.

GENERALIZED INFANTILISM. P. SCHURMANN, Virchows Arch. f. path. Anat. **263**:649, 1927.

A woman, aged 25, was 143 cm. tall and weighed, before her final illness, 46.2 Kg. The psyche was infantile; she had never menstruated, and the secondary sexual characters were not developed. She died in diabetic coma. The chief observation at necropsy was absence of both ovaries, congenital in origin. This was held to have led in turn to the hypoplasia of the pineal, thyroid and pancreas, to the hypertrophy of the hypophysis, and to the generalized microsomia also noted at necropsy.

O. T. SCHULTZ.

IDENTIFICATION CHARACTERS OF SINGLE OVUM TWINS. H. W. SIEMENS, Virchows Arch. f. path. Anat. **263**:666, 1927.

Siemens has devoted much attention to the pathology of twins. He does not believe that the fetal membranes give an absolutely certain clue as to the single ovum origin of twins, nor that the finger prints are of any value in determining such origin of any pair of twins. The condition of the fetal membranes is not of help after birth, since the individual usually has no knowledge of this point. In the study of geminal pathology, it is important to know in any given case whether the twins have come from a single ovum or from two. Siemens maintains that the origin of any given pair of twins from a single ovum can be deduced by comparison of a sufficiently large number of external characteristics, of which he has selected twelve. These are as follows: form and color of the hair; color of the eyes and skin; distribution of freckles; distribution of congenital anomalies of the skin vessels, such as telangiectasis, cutis marmorata and acroasphyxia; keratoses and folliculitis; grooves of the tongue and tooth form; face and head form; ear form; hands and nails; body form. To these so-called dermatologic identification characteristics, which he had previously used, he now adds three others which should be taken into consideration in any study of twins. These are psychic characteristics, congenital anomalies and diseases, and those characters which require for their detection more complicated methods, such as dactyloscopy, capillary microscopy and eye refraction.

O. T. SCHULTZ.

ICTERUS NEONATORUM OF CALVES. E. METZGER, Virchows Arch. f. path. Anat. **263**:703, 1927.

Icterus was present in 504 of 4,000 calves examined by the author. In 322 new-born calves included in the whole series, icterus was detected in twenty-four and the latter group was subjected to microscopic study. The author claims that in these animals the liver was not fully developed, a condition which manifested itself by irregularity of the liver cords and of the bile canaliculi. Metzger concludes that the icteric state is due to the persistence of the fetal condition of the liver, which permits bile pigment to enter the blood.

O. T. SCHULTZ.

DEVELOPMENTAL POTENTIALITIES OF THE MYELOBLAST. A. D. TIMOFEJEWSKY and S. W. BENEWOLENSKAJA, Virchows Arch. f. path. Anat. **263**:719, 1927.

As the result of the study of tissue cultures of blood derived from a patient with myelogenous leukemia, the authors state that the myeloblast is an indifferent cell which may give rise to granulocytes, free and fixed histiocytes, fibroblasts, and possibly small lymphocytes. The explanted cells could be kept alive for more than a month. The chief difference between myeloblasts and lymphocytes in tissue culture is the ease with which granulocytes develop from myeloblasts, whereas the authors claim that a similar transformation of lymphocytes of normal blood has never been seen.

O. T. SCHULTZ.

STRUCTURE OF THE ERYTHROCYTE. M. GUTSTEIN and G. WALLBACH, Virchows Arch. f. path. Anat. **263**:741, 1927.

Through the use of special staining methods, the authors deny the homogeneity of the erythrocyte and describe for this cell the following structures: An outer distinct membrane, composed of a thin outer layer and a thicker inner layer with an intervening chromophobe zone; hemoglobin, which makes up the bulk of the cell; an inner body, within which is a distinct central corpuscular element, and an eccentric microgranule. The inner body with its central corpuscle is held to be the remnant of the nucleus.

O. T. SCHULTZ.

LIPOID STORAGE IN DIABETES. M. A. GOLDZIEHER, Virchows Arch. f. path. Anat. **263**:769, 1927.

In a diabetic patient, aged 24, the reticulum cells of the splenic pulp, the Kupffer cells of the liver and the endothelial cells of the suprarenals were filled with lipoid material. The liver cells and the parenchyma of the suprarenals contained little fat. The deposition of the material in the reticulum cells of the spleen, which the author erroneously claims not to have been previously noted in diabetic lipemia, is looked on as an elective activity of the cells. Since the fat disappeared from the liver and suprarenals and was deposited in the reticulo-endothelial system, the author terms the condition described by him fat metastasis, which he believes to be due to endocrine disturbance for which the suprarenal is held responsible.

O. T. SCHULTZ.

GYNECOMASTIA ASSOCIATED WITH TESTICULAR CHANGES. HELENE HERZENBERG, Virchows Arch. f. path. Anat. **263**:781, 1927.

The author reports three cases of acquired bilateral enlargement of the mammary glands in men aged, respectively, 25, 33 and 24 years. In the first patient, who had hypospadias, atrophy of the testes occurred as the result of diffuse melanoblastomatosis of the scrotum; the interstitial cells were prominent and well preserved. In the second case bilateral inguinal hernia had led to atrophy of the testes, the interstitial cells being reported as hyperplastic. The enlargement of the breasts was held to be due not to activity of the

interstitial cells, but to disappearance of the seminal epithelium and loss of a hormone necessary for maintenance of the masculine secondary sexual characteristics. The increase in the size of the breasts was due to hyperplasia of the stroma and epithelium, with the formation of typical acini. The third patient had a metastasizing tumor of the left testis, the neoplasm being termed a chorio-epithelioma. The breasts began to enlarge two weeks before death. On microscopic examination, their stroma was found to have been transformed into cells of decidual type, a change which was considered a specific reaction to the chorio-epithelioma. The interstitial cells of the right testis were not increased in number but were enlarged and decidua-like.

O. T. SCHULTZ.

FIBRINOUS BRONCHITIS. A. STAPF, Virchows Arch. f. path. Anat. **263**:800, 1927.

Idiopathic fibrinous bronchitis is defined as the condition in which, with the expectoration of more or less complete casts of the bronchi, there is no antecedent history of diphtheria or fibrinous pneumonia. The author reports in great detail the results of the microscopic study of the casts, lungs and bronchi in such a case. In this case, there was a bilateral disseminated alveolar tuberculosis. The bronchi and bronchioles were the seat of subacute and chronic inflammatory changes, with evidences of marked overactivity of the bronchial mucous glands. Hypersecretion of tenacious mucus, usually as the result of a low-grade inflammatory process, is held to be the chief factor in the formation of the bronchial casts which characterize the condition under discussion. For this reason the author proposes the name, plastic mucoid bronchitis, as preferable to fibrinous bronchitis. Fibrin may be present, but only as the result of admixture from a fibrin-containing alveolar exudate.

O. T. SCHULTZ.

VARIATIONS OF THE HUMAN SPLEEN WITH AGE. T. HELLMAN, Ztschr. f. d. ges. Anat., Abt. 2, Ztschr. f. Konstitutionslehre **12**:270, 1926.

In order to determine variation of weight, the relative amount of stroma and changes of the lymphoid tissue with relation to and function of the malpighian bodies, the spleens from 100 bodies of persons murdered or dead from suicide or accident were studied. Paper sections duplicating those from the spleen after paraffin infiltration were used, the various components being enlarged eighteen times. With the weight of the spleen known, the weight, size, shape and other details of its constituent structures were readily estimated.

Up to the ages of 20 or 30, the malpighian bodies increase in weight; they decrease after 50, and reach their highest development in childhood. Their number increases up to puberty, and they are fewer in females. The diminution in number in the spleens of persons committing suicide is assigned to lessened nutrition. The relative weight of the lymphoid tissue was alike in suicide and accidental death, and Hellman seriously questions the possibility of distinguishing a constitutional hyperplasia of lymphoid tissue such as is said to occur with status lymphaticus from that due to other causes. The normal growth of the lymphoid tissue in the spleen resembles the reaction of tissues to poisons, as it is known to occur elsewhere.

LOUISA BACON.

TUBERCULOSIS OF THE URETHRA. H. KUDLICH, Ztschr. f. Tuberk. **48**:115, 1927.

In a boy, aged 5 months, a caseous cavernous primary focus in the apex of the left lower lobe and multiple hematogenous metastases were found. Special attention was given to a caseous focus, the size of a bean, in the corpus-cavernosum of the urethra. Since the rest of the urogenital tract did not show any tuberculous foci, a descending infection could be excluded. The urethral focus is interpreted as a hematogenous metastasis, and the case is reported on account of the rarity of this localization.

MAX PINNER.

MICROHISTOCHEMICAL GOLD REACTIONS ON TUBERCULOUS PATIENTS TREATED WITH "SANOCRYSIN." J. A. GALLINAL, Ztschr. f. Tuberk. **48**:433, 1927.

The organs of six patients who had been treated with "Sanocrysin" were examined according to the microchemical method developed by Christeller and Kurosu for the demonstration of gold in tissue sections. In all cases, gold could be demonstrated. Its distribution was not regular and did not show any definite relation to tuberculous foci. In all cases, gold was found in the Kupffer cells of the liver. Gold was found also regularly in the tubular apparatus of the kidney and in the glandular tissue of the intestine.

MAX PINNER.

EIGHT CASES OF HEMIHYPERTROPHY. EJNAR LENSTRUP, Acta Paediat. **6**:205, 1926.

The anomaly of hemihypertrophy seems to be found with equal frequency in both sexes. It affects the right side a little more often than the left. All of Lenstrup's cases involved both the upper and the lower extremities. Next in frequency of involvement were the external genitalia, the trunk, face, ear and tongue. The bones were involved in three of the eight cases. Several patients were followed from infancy through puberty; one was followed for nineteen years. The difference in size between the two sides of the body remained unaltered. The hypertrophied limbs exhibited poor coordination, although the muscles were highly developed. With the exception of one case, the glands of internal secretion were normal. Mentality was normal with a single exception. An analogy is drawn between this disease and an anomaly observed in fishes in which the preganglionic sympathetic tracts did not cross. Damage to these tracts on one side will affect the development of only one side of the body. In this connection it is of interest that one of Lenstrup's cases was not congenital, but developed at the age of 2 years with the appearance of metastasis from a malignant tumor.

THE PRIMARY COMPLEX IN TUBERCULOSIS OF CHILDREN. JOHN NAESLUND, Upsala Läkaref. Förh. **32**:299, 1927.

Lungs with the so-called "primary complex" lesions of tuberculosis were obtained from twenty children and young persons during five years at the Pathological Institute at Upsala. The disease in the lungs as well as the related disease elsewhere in the bodies is described with great detail. The average age was 5 or 6 years, with a variation of from 2 months to 21 years. Three patients had a definite history of exposure; eight others, a possible infection through relatives, and nine did not have a history of exposure.

The pulmonary disease was not evident during life from physical examination, and roentgenograms in five did not give evidence of primary foci. Lumbar punctures lowered the pressure of the spinal fluid from 60 to 110 mm. It had the characteristics commonly encountered in tuberculous meningitis in the nineteen patients who died with this complication. In nineteen of the twenty, the first infections had occurred in the lungs, thirteen in the right, five in the left, and one had a primary focus in both lungs; thirteen foci were subpleural, six in the parenchyma. The corresponding lymph glands were greatly enlarged and caseous. In the twentieth patient, the tuberculosis had its origin in the bowel in an ulcer 70 cm. above the ileocecal valve. In fifteen others the intestine was without change, but in three, the mesenteric glands were caseous. Miliary tubercles were found in the spleen and liver in ten. The usual structural alterations of tuberculous leptomeningitis were present in seventeen (complete postmortem examinations were not obtained in two).

Grossly the primary foci were irregular, circumscribed regions of caseous pneumonia, which ranged in size from that of a millet seed to that of a dove's egg. Tuberculous cavities were rare and small. Microscopically the caseous

portions were surrounded by granulation tissue and between these there was a zone that was homogeneous and stained with eosin. The lymph glands had similar changes. There was beginning cicatrization of the primary focus in the lungs of a child, aged 11½ years, and complete scarring in those of a man, aged 21. In three the intestines had microscopic tuberculous changes.

Naeslund concludes, as others have, that in the lungs the disease begins as a minute region of pneumonia. It is apparent, when the disease progresses to systemic infection and death, that the changes in the lungs are similar to those of acute pneumonic phthisis developing later in life in persons who have at the same time one or more healed "primary complexes."

LOUISA BACON.

Pathologic Chemistry

THE CYSTINE CONTENT OF HAIR AND OTHER EPIDERMAL TISSUES. R. H. WILSON and H. B. LEWIS, J. Biol. Chem. **73**:543, 1927.

The cystine content of human hair ranges from 15.6 to 21.2 per cent; of sheep wool, from 8.0 to 10.9 per cent; feathers, 7.05 to 12.2 per cent; rabbit hair, 11.9 to 14.0 per cent; tortoise shell, 6.4 to 8.1 per cent; rat hair, 14.1 per cent; cat hair, 13.1 per cent and dog hair, 19.0 per cent. The cystine content of human skin and connective tissues varies from 1.8 to 2.3 per cent. There is no evident relationship between the cystine content of human hair and the color of the hair, the age or the sex of the person from whom the sample is taken.

ARTHUR LOCKE.

THE EFFECTS OF RESPIRATORY GASES UPON THE DENSITY OF BLOOD AND OTHER FLUIDS. W. F. HAMILTON and H. G. BARBOUR, J. Biol. Chem. **74**:553, 1927.

A given amount of carbon dioxide increases the density of certain fluids in this order: Water < alkali-salt solution < serum < blood. Oxygen causes a still greater increase in the density of blood. The physical chemistry of these observations is discussed.

AUTHORS' SUMMARY.

THE EFFECT OF SERUM UPON THE GERMICIDAL ACTION OF SOAPS. ARNOLD H. EGGERTH, J. Exper. Med. **46**:671, 1927.

The action of serum on soaps may be regarded as a complex reaction, in which lipoids, protein, and, to a lesser extent, calcium salts take part. Their effect is due to the fact that these substances, by combining with the soaps, remove them from the field of germicidal action.

A FOREIGN PROTEIN FROM THE PLACENTA IN NEPHROSIS OF PREGNANCY. ERNST SCHWARZCOFF and HERMANN SIEVERS, Deutsche med. Wchnschr. **53**:1303, 1927.

The protein was found in the placenta in a case of nephrosis in pregnancy. This protein resembled the Bence-Jones protein but showed also some differences. The protein was insoluble in hot water but went into solution on cooling.

COPPER IN HUMAN SERUM. O. WARBURG, Klin. Wchnschr. **6**:1094, 1927.

In the human blood serum Warburg found copper constantly in amounts of from 0.1 to 0.2 mg. per hundred cubic centimeters. For its estimation he developed a micromethod which allows the determination of iron, copper and manganese in amounts little larger than 0.00001 mg. Cysteine is placed in a chamber containing the serum and a buffer; then it is shaken with air and the speed of absorption of oxygen is observed manometrically. The cysteine is oxidized only in the presence of iron, manganese or copper. Manganese is

recognized by addition of hydrocyanic acid. Copper is present, if the oxidation is not inhibited by sodium pyrophosphate.

CALCIUM METABOLISM IN DIABETES. ESKIL KYLIN, Acta med. Scandinav. **66**:197, 1927.

In diabetic patients Kylin found 12.1 mg. of calcium (as oxide) per hundred cubic centimeters of blood; for healthy persons, the figures are 11.1. Insulin lowers the calcium content of blood and increases that of the urine.

Microbiology and Parasitology

TRANSMISSION OF TUBERCULOSIS THROUGH DOMESTIC ANIMALS. LYDIA RABINOWITSCH-KEMPNER, Am. Rev. Tuberc. **15**:419, 1927.

In pulmonary phthisis of man mostly human bacilli are found; in abdominal tuberculosis, in tuberculosis of the lymph nodes and bone and especially of the skin, either bovine or atypical tubercle bacilli have been shown to be the cause in many cases. Consumptive people must be looked on as the principal source of infection with human tuberculosis. It is difficult to tell, in practice, where infection by droplet ceases and infection by dust begins. It is not considered impossible that the various types, if remaining in the human body for a long time, may not occasionally change their biologic properties. Not only human tuberculosis, but also that of animals, is a danger to man.

H. J. CORPER.

THE SIGNIFICANCE OF COUGH DROPLETS AND DRY DUST IN THE SPREAD OF TUBERCULOSIS. F. NEUFELD, Am. Rev. Tuberc. **15**:609, 1927.

This is a discussion of droplet and dust infection in tuberculosis. The author concludes that further research will have to decide the frequency of either of these, it having been established that they are equally dangerous in both forms and should be guarded against.

H. J. CORPER.

EXERIMENTAL TUBERCULOSIS IN RATS ON VARIED DIETS: III. SALT FACTORS. LINDA B. LANGE, Am. Rev. Tuberc. **15**:629, 1927.

Five groups of ten rats each were put on diets of different salt content (sodium chloride and calcium carbonate) infected with bovine tubercle bacilli and autopsied at intervals of from one to six weeks. Essential difference in the tissue response to the bacillus was not observed between animals on control diet and on a diet deficient in salt. No constant variation in the gross or histologic picture was demontrated with any of the deficient diets.

H. J. CORPER.

PARENCHYMAL PULMONARY TUBERCULOSIS IN CHILDREN. COLE B. GIBSON and WILLIAM E. CARROLL, Am. Rev. Tuberc. **15**:665, 1927.

Tuberculous parenchymal lesions occur in about 10 per cent of children diagnosed as tuberculous. The mortality of children under 15 years of age suffering with parenchymal tuberculosis is higher than that of adults. Except for the infantile group, girls at the age of puberty reveal the highest of all death rates from pulmonary tuberculosis. The behavior of children with definite tuberculosis of the lung differs somewhat from that of adults similarly affected; they have fewer symptoms and complications than adults but the death rate is higher. More than twice as many girls as boys are so afflicted. The most frequent location of the disease was in both upper lobes; when confined to one lung it was most often right sided. Complications were few but of ill omen. The presence of tubercle bacilli in the sputum of children almost always renders a chance for recovery hopeless.

H. J. CORPER.

AN EXPERIMENTAL INVESTIGATION AS TO A POSSIBLE ETIOLOGIC RELATIONSHIP OF MONILIA PSILOSIS TO PERNICIOUS ANEMIA. A. S. WARTHIN, Ann. Clin. Med. **5**:808, 1927.

Warthin undertook to confirm or disprove the experimental work of E. J. Wood, who had previously concluded that the close similarity between pernicious anemia and sprue clinically suggests the possibility of the two being manifestations of the same disease, that *Monilia psilosis* can be recovered from the feces in both conditions, and that the feeding of cultures and the intravenous injection of dextrose-water filtrates of such yeasts produces an hemolytic anemia. Using three different strains of *Monilia psilosis*, Warthin repeated Wood's experiments in a much larger series of animals. There was no evidence that the ingestion of the *Monilia* or the intravenous injection of filtrates produced hemolytic action in any of the animals. In order to determine whether or not *Monilia psilosis* possessed any pathogenic qualities, intravenous injections of living cultures were carried out. Only one strain, that obtained from a proved case of tropical sprue, produced embolic colonies in the organs, but did not give any evidence of any toxic or hemolytic action. In so far as the etiologic identity of sprue and pernicious anemia, and the ability of *Monilia psilosis* to produce hemolytic anemia are concerned, Warthin's observations are wholly negative and do not provide any support for Wood's contentions.

WALTER M. SIMPSON.

MYCOTIC WARTS. A. PENA CHAVARRIA and P. G. SHIPLEY, Bull. Johns Hopkins Hosp. **41**:11, 1927.

A mother and two children had warts on the fingers. From the warts of the mother was isolated a fungus belonging to *Fungi imperfecti*, and only very slightly, if at all, pathogenic for lower animals.

ON THE BEHAVIOR OF GRANULATING WOUNDS OF THE RABBIT TO VARIOUS TYPES OF INFECTION. CHARLES R. L. HALLEY, ALAN M. CHESNEY and IRMGARD DRESEL, Bull. Johns Hopkins Hosp. **41**:191, 1927

When granulating wounds (from 11 to 16 days old) of the rabbit, after removal of the crust, were inoculated with cultures of *Streptococcus erysipelatis*, the surrounding area of skin showed little or no sign of an acute inflammatory reaction in the succeeding days whereas when fresh wounds in the same animal were inoculated in an identical manner with the same culture the surrounding skin showed signs of an intense inflammatory reaction which persisted for a number of days. A similar, although less marked, difference, was observed between the behavior of granulating wounds and that of fresh wounds after inoculation with *Staphylococcus aureus*. Bacteriologic study indicated that in the case of the granulating wounds the bacteria quickly disappeared from the surface of the granulating area, but did not do so in the case of the fresh wounds. Histologic study failed to reveal the presence of bacteria in the deeper portions of the granulating area, but they could be demonstrated well below the surface of the fresh wounds. It was not possible to demonstrate in extracts of granulation tissue of the rabbit the presence of any lytic principle similar in its mode of action to bacteriophage. When granulating wounds of the rabbit were inoculated with broth cultures of *Pasteurella avicida* the organisms were able to make their way into the circulation and kill the animals in nearly every instance, even when the greatest care was exercised not to disturb the granulating area. On the basis of the data afforded by these experiments and by others in which syphilitic virus was used for inoculation, it is concluded that granulation tissue in the rabbit appears to constitute a relatively unfavorable environment for the survival and growth of streptococci and staphylococci, whereas it appears to offer a favorable locus for the survival of the treponemes of syphilis. This difference in behavior of granulation tissue in the rabbit to different kinds of pathogenic micro-organisms makes it difficult, if not impossible, to formulate a

general principle, applicable alike to all types of bacteria, regarding the susceptibility of granulating wounds to bacterial infection.

AUTHORS' SUMMARY.

FURTHER STUDIES ON STAPHYLOCOCCUS BACTERIOPHAGE. BASSIE R. CALLOW, J. Infect. Dis. **41**:124, 1927.

By passing a staphylococcus suspension in distilled water through Berkefeld filter, a bacteriophage was obtained that was free from broth constituents and did not give any protein color tests. Adding any one of several salts in concentration greater than hundredth molar proved injurious to the bacteriophage, the activity of which decreased as the valence of the anion or cation of the salt increased. Changing the H-ion of the distilled water from p_H 5.4 to 8 increased the strength of the bacteriophage several hundred times. Bacteriophage was not precipitated by absolute alcohol or acetone. Heat at 60 C. for half an hour and various chemicals, destroyed the bacteriophage. Chloroform (0.6 per cent) sterilized the water without injuring the bacteriophage, but toluene and tricresol (0.5 per cent) were injurious, while ether had no effect. Kaolin and alumina cream adsorbed the bacteriophage; under certain circumstances, small amounts could be eluted from the kaolin only. Collodion sacs made with ether (40 parts) and alcohol (60 parts) withheld the bacteriophage while more permeable sacs allowed rapid diffusion.

AUTHOR'S SUMMARY.

LEPTOSPIRAS FROM TAP WATER. JOHN E. WALKER, J. Infect. Dis. **41**:164, 1927.

Leptospiras from Washington tap water grow profusely in mixed culture in a medium consisting of egg yolk, 1:300, in 0.3 per cent agar. The presence of *B. coli* in the medium is favorable to the development of the organisms. The necessity for shallow layers of the medium in Petri dishes is apparently related to the fact that the medium in deeper layers acquires an acid reaction.

No evidence of pathogenicity was demonstrated in the organisms so cultivated. Pathogenic leptospiras in the agar-egg yolk medium survive for from ten to thirty days. There is, however, no clear evidence of multiplication, and no growth occurs in successive transfers. This latter feature, under the conditions of these experiments, forms a sharp line of demarcation between the water organisms and pure cultures of strains derived from humans.

AUTHOR'S SUMMARY.

IS DIABETES OF INFECTIOUS ORIGIN? E. GUNDERSEN, J. Infect Dis. **41**:197, 1927.

Deaths from diabetes mellitus in Norway during 1898 to 1921, when distributed in various age groups, form two distinct intersecting curves, one representing early life and culminating at puberty, the other representing more advanced ages leading up to the 60 to 70 years' group, the total number of deaths recorded being 5,951. Mortality curves for men and women follow parallel lines in the younger and older age groups.

Etiologic factors influencing diabetes in the older age group are race, heredity, obesity, arteriosclerosis, nervousness and disturbances of internal organs; in the younger age group infections such as scarlatina, typhoid fever and epidemic parotitis, with subsequent parotitic pancreatitis, often lead to grave and rapidly fulminating diabetes.

Parotitic epidemics in the young age group are followed by a rise in the death rate from grave diabetes in the young age group three to four years following each successive parotitic epidemic. Atrophy of testicles following parotitic orchitis is similar in nature to atrophy of pancreas following parotitic pancreatitis.

"Acute diabetes" in youth, graver in type and more rapidly fatal than slower and milder development of diabetes in the older age group, is suggested by the author to be infectious in origin and probably caused by the virus producing epidemic parotitis.

AUTHOR'S SUMMARY.

ANAEROBIC MICROORGANISMS IN NASOPHARYNGEAL WASHING. SARA ELIZABETH BRANHAM, J. Infect. Dis. **41**:203, 1927.

Nasopharyngeal washings from twenty-six persons, including thirteen with colds, five with acute influenza and eight normal persons, were examined by the technic of Olitsky and Gates. From eleven of these samples seventeen strains of anaerobic micro-organisms were isolated, thirteen of which seem to belong to species previously described. Four strains resembled the gram-negative, gas-producing coccus found abundantly in normal mouths by Holman and Krock and by Hall and Howitt. Two were probably the large granular spirochete of sinus infections which was described by Tunnicliff. Seven were apparently the filtrable micro-organisms reported by Olitsky and Gates: two of these seemed identical with their slender curved group 1 and one with the granular group 3. Four were probably either *Bacterium pneumosintes* or the group 2 which resembles it; three of these came from patients with influenza during March, 1926, and one from a normal person two months after the epidemic had subsided.

The remaining four strains seem to fall into two groups, hitherto undescribed. One of these groups was a minute gram-negative organism of indeterminate morphology. The other, a small gram-negative hemolytic diplococcus, is described briefly here.

AUTHOR'S SUMMARY.

A TOXIN-PRODUCING HEMOLYTIC STREPTOCOCCUS FROM SEPTICEMIA. I. PILOT and R. E. WESTLUND, J. Infect. Dis. **41**:208, 1927.

A strain of streptococcus hemolyticus isolated from the blood of a patient with septicemia produced a toxin which resembled the toxin of streptococci from scarlet fever in skin reactions and in neutralization tests with antitoxic serums. Agglutination reactions and absorption tests, however, failed to demonstrate a similar specific relationship.

AUTHOR'S SUMMARY.

EFFECT OF SURFACE TENSION ON THE GROWTH OF ESCHERICHIA COLI. WILLIAM R. ALBUS, J. Infect. Dis. **41**:211, 1927.

The growth of *E. coli* is affected by the surface tension of the medium as is shown by a reduction in the number of living cells in the culture. The cell mortality does not take place until after the culture has passed through a normal logarithmic growth period. While no explanation is offered concerning the nature of the action which brings about this cell mortality it is shown that it follows the surface tension of the medium rather than the concentration of the depressant.

AUTHOR'S SUMMARY.

GRANULOMATOUS GROWTHS IN THE RAT CAUSED BY B. LEPRÆ-MURIUM. E. MUIR, J. M. HENDERSON and E. LANDEMAN, Indian J. M. Research **15**:15, 1927.

Following the intraperitoneal inoculation of *B. lepræ-murium* there developed in rats granulomatous growths with fibrosis, caseation and liquefaction.

POST-KALA-AZAR DERMAL LEISHMANIASIS. H. W. ACTON and L. E. NAPÚR, Indian J. M. Research **15**:97, 1927.

In generalized infection with *Leishmania donovani* there may develop well marked cutaneous lesions in the form of depigmented patches, nodules and xanthoma-like growths. The tabulated details of forty-four cases are given.

BOVINE PIROPLASMAS. E. SERGENT, A. DONATIEN, L. PARROT, F. SESTOQUARD and E. PLANTUREUX, Ann. de l'Inst. Pasteur **41**:489, 1927.

Rhodesian fever of South African cattle caused by *Theileria parva* is distinct from the North African disease caused by *Theileria dispar*. There is no cross

immunity. *T. dispar* can be transmitted by blood inoculations, but the infection is benign, only occasionally causing a mild anemia and splenomegaly. Morphologic differences in the two types are concerned with the relative proportion of certain forms in the peripheral blood.

G. B. RHODES.

DOES THE TRYPANOSOME OF DOURINE TRAVERSE HEALTHY SKIN AND MUCOUS MEMBRANE? E. IWANOW and F. MESNIL, Ann. de l'Inst. Pasteur **41**:507, 1927.

Experiments led to the conclusion that *Trypanosoma equiperdum* does not penetrate intact skin and membranes. Artificial impregnation is advised as a preventive measure in breeding stables.

G. B. RHODES.

A STUDY OF RINGWORM INFECTION IN HORSES AND IMMUNITY IN EXPERIMENTAL RINGWORM. BROCQ-ROUSSEU, A. URBAIN and J. BAROTTE, Ann. de l'Inst. Pasteur **41**:513, 1927.

The only organ susceptible to infection by the ringworm parasite (usually a microspore) is the skin. Immunity is readily established with living cultures and is in proportion to the extent of the lesion of the skin. Antibodies are easily demonstrable by complement fixation in infected guinea-pigs and to a lesser degree in horses though the reaction is specific. Trichophytin (similar to tuberculin) gives positive skin reactions in 100 per cent of infected animals. Tuberculin also gives positive skin reactions in some of these cases. Some tuberculous persons and animals show positive intradermal reactions with trichophytin.

G. B. RHODES.

RESEARCH ON THE BACTERICIDAL ACTION OF ROENTGEN RAYS. J. J. TRILLAT, Ann. de l'Inst. Pasteur **41**:583, 1927.

Roentgen rays act on *Bacillus prodigiosus* with more force as the length of the wave increases. This action is considerably increased by secondary rays coming from metals of high atomic weights.

G. B. RHODES.

INVISIBLE AND FILTRABLE FORMS OF VISIBLE BACTERIA. P. HAUDUROY, J. de physol. et de path. gén. **25**:254 and 283, 1927.

The filtrable germs are divided into two groups, the group of the filtrable bacteria and spirochetes (*Asterococcus mycoides,* microbes of influenza, *Treponema recurrentis, Treponema venezuelense* and others) and the group of the ultravirus. Then follows a detailed description of the various methods of filtration and a discussion of the theory of filtration and of the factors influencing filtration as reaction of the filtrate, albuminous content, etc. Hauduroy discusses the method and technic of ultrafiltration through collodion sacs. He states the effect of adsorption, reaction of filtrate, presence of alcohol, ether, sugar and other substances in the filtrate on the result of filtration. Collodion sacs are not frequently used for filtration on account of the difficulty in handling, sterilizing and standardizing them. Fontès injected the diluted and filtered content of a cold abscess into a guinea-pig and saw after fifty days chromophil granules in the lymph nodes and spleen of this animal, but no acid-fast bacilli. The guinea-pig into which the spleen was inoculated, after five months had a tuberculosis of the lung and tubercle bacilli could be demonstrated. Philibert repeating these experiments concluded that neither the bacilli nor the granules pass the filter. Vaudremer and subsequently Hauduroy culturing tubercle bacilli on media containing little nitrogenous substances observed the formation of nonacid-fast bacilli and granules of various forms. In the filtrate of these cultures growth of nonacid-fast elements was noticed, which formed anastomosing filaments, occasionally also rods. Acid-fastness of these rods was rarely seen. Subcutaneous injection of the filtrate produced a temporary local indura-

tion. Intravenous administration caused a generalized polyadenitis. Acid-fast granules were found in cultures of the pus from softened lymph nodes, from which in subsequent cultures typical Koch's bacilli could be developed. The injection of cultures of the granular forms resulted either in death of the animals without producing tuberculous manifestations or caused in the surviving animals an immunity, which was demonstrated by their resistance to the injection of massive doses of tubercle bacilli. The acid-fast form of the tubercle bacillus is regarded by Hauduroy as only one form in which this bacillus exists. The bacillus could be transformed through proper treatment from the acid-fast form through a nonacid-fast and granular form into an invisible, filtrable form and back to the acid-fast form. The immunity was regarded as the result of an atypical tuberculosis caused by the injection of the granular form. Calmette, Valtis and others succeeded in demonstrating the passing of the tubercle bacillus through the placenta into the fetus by injecting the peritoneal exudate of a tuberculous guinea-pig into a pregnant one. Tuberculosis was found in lymph nodes of the offspring. The injection of filtrable virus had the same effect according to Arloing and Dufourt.

W. C. Hueper.

The Effect of Sodium Aurothiosulphate and Møllgaard's Serum on Guinea-Pigs. K. Weise and E. Jakobssohn, Beitr. z. Klin. d. Tuberk. **66**:144, 1927.

On the foundation of extensive animal experimentation the following conclusions are drawn: there is no difference in the action of sodium aurothiosulphate on the healthy, or on the tuberculous organism. The phenomena elicited by injections of sodium aurothiosulphate are not tuberculotoxic in nature but are the manifestation of a metal poisoning. The serum, according to Møllgaard, has no effect on the toxic action of sodium aurothiosulphate, neither in the normal, nor in the tuberculous guinea-pig. It has no detoxifying properties in regard to the tuberculin shock in tuberculous animals. No therapeutic results were obtained with sodium aurothiosulphate on tuberculous guinea-pigs.

Max Pinner.

The Significance of the Sedimentation Reaction in Tuberculosis. F. Langebeckmann, Beitr. z. Klin. d. Tuberk. **66**:172, 1927.

If the results of the sedimentation reaction fit the clinical picture they constitute a valuable aid for prognostication. If, however, the sedimentation values are constantly high, although the clinical condition of the patient appears to be good, a thorough investigation should find unsuspected cause for the increased sedimentation rate.

Max Pinner.

The Viscosity of the Blood in Pulmonary Tuberculosis. G. Schnierelmann, Beitr. z. Klin. d. Tuberk. **66**:183, 1927.

In pulmonary tuberculosis the viscosity of the blood goes parallel with the degree of the tuberculous toxemia, with the sedimentation rate of the red cells, and with the number of erythrocytes. The hemoglobin and the number of leukocytes do not have any influence on the viscosity in pulmonary tuberculosis.

Max Pinner.

The Behavior of Blood Sedimentation After Provocatory Tuberculin Administration. K. Stetter, Beitr. z. Klin. d. Tuberk. **66**:387, 1927.

After injection of tuberculin the sedimentation rate practically never increases in the absence of signs indicative of tuberculosis. Patients with tuberculous pulmonary foci behave differently in this regard. In active tuberculosis the increase of the sedimentation rate is obtained more frequently than in inactive cases, but the differentiation between active and inactive tuberculosis by this method alone is not possible.

Max Pinner.

THE FORMATION OF TUBERCULOUS FOCI AFTER INTRATRACHEAL INFECTION OF RABBITS. W. PAGEL, Beitr. z. Klin. d. Tuberk. **66**:423, 1927.

Following intratracheal infection the focus is more of the multilocular type than after infection by inhalation. Small single foci conglomerate to one focus. The evolution of these foci is less regular than those produced by inhalation infection. The dose of infection and the virulence plays an apparently important rôle in the resulting morphology.

MAX PINNER.

THE INFLUENCE OF SODIUM AUROTHIOSULPHATE ON EXPERIMENTAL TUBERCULOSIS IN RABBITS. OPITZ, KOTZULLA, and WÄTJEN, Beitr. z. Klin. d. Tuberk. **66**:441, 1927.

As a result of extensive and carefully controlled experiments, the authors come to the conclusion that sodium aurothiosulphate does not influence the evolution of an acute, or chronic, tuberculous infection in rabbits. No definite histologic differences could be detected in treated and nontreated animals. Not even if treatment with sodium aurothiosulphate is started immediately after the infection does it exert a favorable influence. The disagreement of these results with those published by Møllgaard is explained by the difference in virulence of the strains used.

MAX PINNER.

THE PENETRATION OF INFECTIOUS AGENTS INTO REGIONAL LYMPH NODES AND INTO THE CIRCULATION AFTER CUTANEOUS INFECTION. ALBRECHT SCHMIDT-OTT, Ztschr. f. Hyg. u. Infektionskr. **107**:441, 1927.

Trypanosomes, spirochetes and certain bacilli after cutaneous inoculation are found in the regional lymph nodes within a short time, sometimes within a few minutes. They enter the blood later, but before they can be discovered in remote lymph nodes. The rapidity of dissemination to the regional lymph nodes does not depend on the size, the motility or the virulence of the infectious agents, while in the penetration into the blood stream the virulence plays a decisive part. The experiments seem to demonstrate a certain protective action on the part of the regional lymph nodes against the further dissemination of the infection in the animal organism.

W. OPHÜLS.

THE RÔLE OF THE RETICULO-ENDOTHELIUM IN CURES BY CHEMOTHERAPEUTIC AGENTS. ADOLF FELDT and ALIX SCHOTT, Ztschr. f. Hyg. u. Infektionskr. **107**:453, 1927.

Like Jungeblut of the George Speyer House at Frankfort these investigators who are attached to the staff of the Koch Institute in Berlin also came to the conclusion that interference with the reticulo-endothelial system in mice infected with recurrens spirilla or trypanosomes distinctly decreases the therapeutic efficiency of such chemotherapeutic agents as arsphenamine, neoarsphenamine, acriflavine, Bayer 205.

W. OPHÜLS.

ATTEMPTS AT INFECTION WITH SINGLE "ANIMAL" ANTHRAX-BACILLI. GEORG ZOLTÁN MARTOS, Ztschr. f. Hyg. u. Infektionskr. **107**:477, 1927.

The bacilli used in these experiments were obtained directly from infected animals. The mortality according to the infectious dose varied as follows: Of ten mice infected with twenty bacilli ten, or 100 per cent, died; of eleven mice infected with ten bacilli eight, or 73 per cent, died; of twenty mice infected with five bacilli thirteen, or 65 per cent, died; of twenty mice infected with two bacilli ten, or 50 per cent, died, and of fifty mice infected with one bacillus fourteen, or 28 per cent, died. The length of life of the killed animals varies from two to four days in animals infected with twenty bacilli from three to nine days in animals infected with a single bacillus.

W. OPHÜLS.

GOLD TREATMENT IN EXPERIMENTAL TUBERCULOSIS OF RABBITS. O. BANG, Ztschr. f. Tuberk. **47**:286, 1927.

The author repeated in every detail the experiments published by Madsen and Mórch. His results were completely negative. Eighteen rabbits, in which treatment with sanocrysin was started from four to five days after the injection, died of tuberculosis in an average of eighty-five days after infection. Fifteen rabbits in which treatment was started immediately following the infection lived an average of 108 days. Nineteen control animals that did not receive treatment lived an average of 105 days.

MAX PINNER.

GRAVE TUBERCULOSIS IN CHILDREN AND THE RELATIONS BETWEEN TUBERCULOSIS IN CHILDREN AND THE LATER CHRONIC PULMONARY TUBERCULOSIS. R. ZIMMERMANN, Ztschr. f. Tuberk. **47**:353, 1927.

On the basis of observations on about 100 children with severe tuberculosis, the following conclusions are reached. School attendance is apt to have an unfavorable influence on tuberculous children. Acute infectious diseases hasten the unfavorable outcome in tuberculous children. In children and adolescents from tuberculous families, the rather benign cirrhotic types are more frequently observed. It appears that children from such families have as a rule a better prognosis than patients from tuberculosis-free families. The placental transmission of tuberculosis should again be investigated. The anatomic differences between the primary pulmonary focus and foci of reinfection are not cleancut. In a general way the primary focus is poorly vascularized, surrounded by a gray capsule, frequently calcified, and located in normal lung tissue. The focus of reinfection has a richly vascularized black capsule, it calcifies much more rarely and is found in atelectatic tissue. The first manifestations of pulmonary tuberculosis in childhood are predominantly of the type of infiltrations. The beginning propagation of tuberculosis in the lung occurs mainly by blood and lymph stream. Tuberculosis at school age shows not infrequently the typical apical-caudal progression and may be of the cirrhotic cavernous type. The differences between tuberculosis in second childhood and that of adult age are differences of quantity and not of quality. During the premenstrual years there is a definite tendency for exudative manifestations.

MAX PINNER.

LATE CASEATION OF LYMPH GLANDS AND RANKE'S STAGES IN TUBERCULOSIS. H. BEITZKE, Ztschr. f. Tuberk. **47**:449, 1927.

Four cases of tertiary phthisis in adults are reported in which some of the hila of the glands showed the type of extensive caseation which is usually found only in the initial period. Similarly, cases are reported with extensive caseation of other groups of lymph glands. These processes are interpreted as manifestation of a completely broken down resistance. On the foundation of the cases mentioned, it is recommended to abandon Ranke's three stages and to differentiate only a primary period and reinfection period in tuberculosis.

MAX PINNER.

STUDIES OF THROMBOCYTES IN PULMONARY TUBERCULOSIS. L. VAJDA, Ztschr. f. Tuberk. **48**:235, 1927.

In pulmonary tuberculosis the thrombocytes are quantitatively and qualitatively changed in comparison with the normal. In exudative phthisis they are increased in number. In productive processes they are decreased. The qualitative alterations comprise an increase in the very small, in the very large and in the spindle shaped blood platelets, and an increase of the basophil platelets.

MAX PINNER.

A Contribution to the Question of Virulence of the Koch Bacillus. William Böhme, Ztschr. f. Tuberk. **48**:383, 1927.

The process of a methodical decrease of virulence of a hereditary character, such as claimed by Calmette for the B. C. G. strain, is not satisfactorily proved. In immunization experiments the method of creating a depot which will cause a strictly localized infection, is more important than the question of virulence. It is possible to reduce the virulence of tubercle bacilli in a methodical and accurate way by exposing them for various lengths of time to physiologic sodium chloride solution. This procedure is promising of results, as the author has shown in experiments carried out since 1921.

Max Pinner.

Immunology

The Elimination of Specific Substances of the Tubercle Bacillus in Tuberculous Animals. J. Furth, Am. Rev. Tuberc. **15**:723, 1927.

The precipitin reaction may be used to study the elimination of specific substances of the tubercle bacillus from the animal body. The smallest amount of tuberculin, which, when injected into normal or tuberculous guinea-pigs, can be detected as a precipitable substance in the urine of the animal, is 0.1 cc. The precipitable substance present in tuberculin, when injected into the vein of normal or of tuberculous rabbits, rapidly disappears from the circulation and can be recovered from the urine of the animal. When tuberculin is injected into the subcutaneous tissue of normal or tuberculous rabbits the precipitable substance is not present in the blood stream in detectable amounts, but it can be recovered from the urine of the animals.

H. J. Corper.

A Nonprotein Antigen of the Tubercle Bacillus. Max Pinner, Am. Rev. Tuberc. **15**:714, 1927.

The alcohol-soluble, acetone and chloroform-insoluble substances of tubercle bacilli contain an active antigenic principle. The antigenic action of these substances, whose chemistry is not known, is a nonprotein material.

H. J. Corper.

The Refraction and Colloid Lability of the Blood-Serum in Tuberculosis. Julius Darányi, Am. Rev. Tuberc. **15**:510, 1927.

The colloid-lability reaction indicates the activity of the tuberculous process. The determination of both refraction and colloid lability of the serum can be well applied in the conditional diagnosis and the prognosis, especially by means of serial examinations. From the refraction one can estimate the quantity, and from the colloid lability the dispersion of the serum-proteins. Both values express the protein-structure (Eiweissbild). In incipient cases refraction is normal, and colloid lability in most cases becomes positive. In chronic tuberculosis both values are increased. In grave cases, low refraction values occur with strong positive colloid lability. In serial examinations, increase of refraction and colloid lability indicates progression of the tuberculosis, and decrease of both healing. An increase of colloid lability to strongly positive reaction, with a diminution of refraction, that is, an inverse progression of both values, indicates a bad prognosis, especially if hyporefraction values are reached.

H. J. Corper.

The Serological Measure of Tuberculosis. Arthur Vernes, Am. Rev. Tuberc. **15**:505, 1927.

The photometric seroreaction is believed to have practical application in discovering concealed forms of tuberculosis; in observing the evolution and

prognosis of collapse therapy, and the nature of an empyema. The seroreaction is believed to be an indispensable control for all attempts at specific treatment of tuberculosis.

H. J. Corper.

The Vernes Test for Tuberculosis. Adelaide B. Baylis, Am. Rev. Tuberc. **15**:500, 1927.

The Vernes test for tuberculosis, a photometric test for reading flocculation of a serum mixture, promises to be a distinct contribution to the serologic methods in the diagnosis of tuberculosis and as a guide to treatment. The precise technic and mechanically controlled apparatus should tend toward more comparable and accurate results from one or several laboratories on the serum from the same patient. The photometer is illustrated and described, as well as the method in detail.

H. J. Corper.

Blood Groups in Tuberculosis. Theophile Raphael, Olive M. Searle and Tom N. Horan, Arch. Int. Med. **40**:328, 1927.

No specific relationship was found between blood types and tuberculosis.

Transmissible Toxicogenicity of Streptococci. Martin Frobisher and J. Howard Brown, Bull. Johns Hopkins Hosp. **41**:167, 1927.

Nontoxicogenic, nonscarlatinal streptococci and strains of *B. coli*, *B. prodigiosus*, *B. subtilis* and *S. albus* have been cultivated in mixed culture with toxicogenic, scarlatinal streptococci and then recovered in pure culture. Two nonscarlatinal streptococci were found to have acquired, temporarily, a definite toxicogenicity, giving rise to a toxin which is neutralized by anti-scarlatinal serum. The other organisms did not acquire any toxicogenicity. Nontoxicogenic streptococci may acquire a toxicogenicity from sterile Berkefeld filtrates of the scarlatinal types, although the toxicogenic powers so acquired are, in general, less marked than those acquired from the mixed cultures. The existence of a filtrable second factor associated with the scarlatinal streptococci is suggested.

Authors' Summary.

A Further Contribution to the Serology of Typhus Fever. W. James Wilson, J. Hyg. **26**:213, 1927.

The development in typhus fever blood of agglutinins for a bacillus of the colon-paratyphoid group, which was isolated in 1921 from the feces of a patient with typhus is shown to be a frequent occurrence in the disease as met with in Ireland, Poland and Syria. The bacillus has preserved its agglutinability up to the time of writing—a period of five years. Owing to its similarity to a bacillus previously isolated by the writer and which was designated bacillus "U," this bacillus has been named *B. agglutinabilis* "U_2." It has been shown that bacteria preserved in alcohol even for three years are sensitive for use in the serologic test, and that serums to which equal volumes of pure glycerine have been added retain their agglutinins for at least five years. Five strains of *B. proteus* "X 19" fermented salicin with the production of acid and gas. Ordinary proteus strains had no action on this glucoside and neither had the anindologenes strain "Kingsbury" although belonging to the "X 19" group. Strains of *B. proteus* "X 19" show great differences in their sensitiveness to typhus fever agglutinins. Views which have been advanced to explain the Weil-Felix reaction are discussed and the conclusion is reached that to label it as an instance of paragglutination does not account for the rise and fall of the agglutinins—agglutinins which are formed not only for *B. proteus* "X_2" and "X 19," but for certain strains of the *B. pyocyaneus* and colon-paratyphoid-typhoid groups.

Author's Summary.

THE SMOOTH MUSCLE REACTION IN THE SERUM TREATED EARTHWORM. SUSAN GRIFFITH RAMSDELL, J. Immunol. **13**:385, 1927.

The phenomenon of sensitization was obtained in the smooth muscle of the earthworm.

SKIN TESTS TO EXTRACTS OF ECHINOCOCCUS AND ASCARIS. FRANCIS M. RACKEMANN and AMOS H. STEVENS, J. Immunol. **13**:389, 1927.

In patients with echinococcus disease a skin reaction is obtained which is associated with antibodies in the blood. In discussing sensitization to ascaris mention is not made of the important work by Ransom, Harrison and Couch (*J. Agric. Research* **28**:577, 1924 and Ransom, *J. Parasitol.* **9**:22, 1922).

REACTIONS OF THE CIRCULAR MUSCLE OF THE CROP DURING ANAPHYLACTIC SHOCK IN PIGEONS. P. J. HANZLIK and A. B. STOCKTON, J. Immunol. **13**:395, 1927.

RECIPROCAL ACTION OF THE CROP MUSCLES IN ANAPHYLACTIC SHOCK, WITH A NOTE ON THE EFFECTS OF HEPARIN. P. J. HANZLIK, E. M. BUTT and A. B. STOCKTON, ibid. **13**:409, 1927.

The reaction of the muscles of the crop of anaphylactic pigeons agrees with the reaction of smooth muscles of anaphylactic mammals. The mechanism of the hypertonic contraction is local. In the pigeon the circular and longitudinal muscles of the intact crop respond to anaphylactic shock with a reciprocal action, and in this case the functional integrity of the peripheral neuromuscular elements in the crop is essential. Heparin, sufficient to prevent coagulation of the blood, did not prevent the general symptoms of shock or the reciprocal action of the crop muscles in anaphylactic pigeons.

THE INFLUENCE OF HEPARIN ON THE COURSE OF ANAPHYLAXIS IN THE GUINEA-PIG. C. I. REED and R. W. LAMSON, J. Immunol. **13**:433, 1927.

In sensitized guinea-pigs the injection of heparin did not protect against anaphylaxis and did not prevent the positive phase of blood clotting during anaphylactic symptoms. The experiments do not support the idea that embolism plays any part in causing anaphylactic symptoms in guinea-pigs.

THE RELATIVELY HEAT STABLE COMPONENTS OF COMPLEMENT. HUGH ROBINSON WHITEHEAD, JOHN GORDON and ARTHUR WORMALL, J. Immunol. **13**:439, 1927.

Small amounts of ammonia or amines inactivate complement by destroying a heat stable element which is set up as the fourth component of complement.

THE ACTION OF PANCREATIC EXTRACTS ON COMPLEMENT: II. THE RELATIONSHIP BETWEEN PROTEOCLASTIC AND ANTICOMPLEMENTARY POWERS OF DIFFERENT ENZYME EXTRACTS. ARTHUR WORMALL, HUGH ROBINSON WHITEHEAD and JOHN GORDON, J. Immunol. **13**:451, 1927.

The proteoclastic and anticomplementary actions of pancreatic extract appear to be due to one and the same substance.

PRECIPITIN, LYSIN AND AGGLUTININ TESTS WITH BILE. ETHEL B. PERRY, J. Infect. Dis. **41**:21, 1927.

Precipitin reactions of human hemoglobin with gallbladder bile from rabbits killed after single injections of human hemoglobin could not be interpreted as evidence of a true antibody response in the bile, because many nonspecific precipitin reactions were obtained with a variety of hemoglobin solutions and biles, and because the reactions with bile differ so essentially from those with immune serums. Neither normal nor specific precipitin was found in fresh dog bile from either gallbladder or fistula.

Fresh fistular bile from untreated dogs was not agglutinative, but was lytic (both with and without complement) for the red blood cells of goat and of rat. These reactions with bile occurred in low dilutions only, and were unaffected by single intravenous injections of erythrocytes which produced characteristic antibody response in the serum.

AUTHOR'S SUMMARY.

THE PRODUCTION OF DIPHTHERIA ANTITOXIN. ARTHUR LOCKE, E. R. MAIN and F. A. MILLER, J. Infect. Dis. **41**:32, 1927.

The preparation of diphtheria antitoxin serums of high titer requires that the quantities of toxin injected during the course of immunization be large enough to maintain maximum production. An interruption of maximum production may be detected at once by a rapid decrease from the normal in the flocculation time of a trial bleeding. The flocculation time of the plasma ordinarily passes through a minimum value of about six minutes during the first month of immunization and then rises gradually to a value of about two hours at the end of the third month, although it may be maintained at the minimum value by restricting the amounts of toxin injected to quantities which just constitute an antigenic stimulus, or it may reach values upward of four hours when the animal is being undesirably forced.

The avidity of a fresh antitoxin plasma, per unit of titer, is a function of the shortness of its time of flocculation with a given toxin. It has been evaluated for the plasmas drawn during this study and has varied from a maximum of 0.8 to a minimum of 0.5. Correspondingly, it has been found necessary to employ approximately 1.25 L_o units of the former preparation and 2.0 L_o units of the latter preparation to neutralize the toxicity of one L_o unit of toxin when the two were injected intravenously into rabbits immediately after mixture. When the times of injection of the toxin and antitoxin were separated by five minutes, approximately 1.25 x 200 L_o units of the first preparation and 2.0 x 200 L_o units of the latter were required.

AUTHORS' SUMMARY.

THE DEGENERATION OF COMPLEMENT ON STORAGE AT SEVERAL TEMPERATURES. JOHN F. NORTON, BLAKE BARFIELD and I. S. FALK, J. Infect. Dis. **41**:39, 1927.

We have found no evidence of the regeneration of complement during storage over a period of forty-two days at temperatures of 37, 4 to —6, and —10 C. Complement stored at 37 C. deteriorated rapidly. The activity of both undiluted and diluted serum disappeared by the end of the third day of storage at this temperature. Both undiluted and diluted serums retained their original complementary activity for forty-eight hours at 4 to 6 C. At the end of seven days the unit was found to be two to three times as great as that of the fresh serum. Frozen serum kept at —10 C. retained its complementary power for two days, after which deterioration proceeded slowly. The undiluted serum could be used for about two weeks, the diluted serum for not more than five to seven days.

Guinea-pig serum possessed the greatest complementary potency. Swine serum ranked second. Horse and rabbit serums could be used but were less satisfactory. Sheep serum failed to complement the hemolytic system studied, due to the absence of the complementary factor rather than to the presence of interfering substances.

The rate of deterioration of complementary activity could be expressed by use of a monomolecular equation, although it does not necessarily follow that the reaction is monomolecular.

The constants obtained with this equation were approximately the same for the four serums stored at any one temperature, showing that the rate of loss of complementary activity was nearly identical for guinea-pig, swine,

horse and rabbit serums. This may be considered as evidence in favor of the view that the complementary factor is the same, regardless of its source.

AUTHORS' SUMMARY.

STUDIES ON ANTIGEN FOR THE KAHN TESTS: UNIFORMITY IN SENSITIVENESS OF STANDARD ANTIGEN. R. L. KAHN, NATHAN NAGLE and PEARL L. KENDRICK, J. Infect. Dis. **41**:111, 1927.

Different lots of beef heart produce Kahn antigen which may vary in sensitiveness. This is believed to be due, in part at least, to differences in the degree of autodigestion of beef heart, leading to varying lipoid concentrations of the antigen.

Antigen may be standardized to a high degree of uniformity in sensitiveness. An antigen too concentrated in beef heart extractives can be made standard by dilution with alcohol, and one not concentrated enough can be standardized by the addition of a titrated amount of extractives. The procedure for standardizing antigens of varying sensitiveness is given. Antigens prepared and standardized in these laboratories during 1924, 1925 and 1926 were found to be practically alike in sensitiveness.

AUTHORS' SUMMARY.

INTERFERENCE PHENOMENA IN THE ACTION OF CHEMOTHERAPEUTIC AGENTS IN TRYPANOSOME INFECTIONS. C. H. BROWNING and R. GULBRANSEN, J. Path. & Bact. **30**:513, 1927.

The phenomenon of chemotherapeutic interference was originally described by us in the case of a parafuchsin-resistant strain of trypanosomes which in normal mice was susceptible to the trypanocidal action of trypaflavin, but was insusceptible to this agent when the infected animals were previously treated with parafuchsin. The observations of Schnitzer with Rosenberg and Silberstein have been confirmed, viz., (*a*) that the trypanocidal action of other substances, e. g., arsacetin, is also interferred with by parafuchsin, when a subtherapeutic dose of the latter is administered before a therapeutic dose of the former, and (*b*) that it is not necessary to conduct the experiment with a parafuchsin-resistant strain of trypanosomes, since the phenomenon may be observed with a normal strain. Interference with the therapeutic action of sodium acetylarsanilate (arsacetin) is produced by ethylviolet, a tri-aminotriphenylmethane dye related to parafuchsin, whereas tryparosan, belonging to the same group, and Döbner's violet, a diaminotriphenylmethane compound, have only an uncertain interfering effect. Trypan blue, a tetrazo derivative, shows some interfering action. A small dose of parafuchsin interferes with the trypanocidal action of the related substance tryparosan, but does not interfere with a subsequent therapeutic dose of itself. As regards the mechanism of interference, the facts indicate that this is due mainly to the direct action of the parafuchsin on the trypanosomes. The bearing of the observations on Ehrlich's theory of chemoceptors is discussed. It is concluded that, while they are not incompatible with the theory, there is at present no simple explanation of the results.

AUTHORS' SUMMARY.

THE TITRATION OF SCARLET FEVER ANTITOXIN IN RABBITS. H. J. PARISH and C. C. OKELL, J. Path. & Bact. **30**:521, 1927.

By means of a test involving the protection of rabbits against the septicemia produced by the intravenous injection of the scarlet fever streptococcus, it has been found possible to distinguish efficient therapeutic serums from inefficient. The test has been used on a practical basis as a method of titrating antitoxin. Evidence is produced which strongly suggests that the antibody measured in the test is scarlet fever antitoxin and so far as it has been explored the test has been found to run parallel with the usual methods of titrating antitoxin in human subjects.

AUTHORS' SUMMARY.

EXPERIMENTAL INVESTIGATIONS OF CHANCROID INFECTIONS. P. TEISSIER, J. REILLY and E. RIVALIER, J. de physiol. et de path. gén. **25**:268, 292 and 319, 1927.

The authors prepared from cultures of Ducrey's streptobacillus after the method of Besredka for preparation of endotoxins and antigen, the "crude streptobacilline." The antigenic elements of this substance were found to be bound to the nucleoproteins and globulins. On account of the high toxicity of the nucleoprotein fraction, this part was separated from the globulin fraction, which was tolerated very well by the animals injected with the antigen and which was called purified "streptobacilline." The antibody formation is more marked after intravenous injection than after subcutaneous injection of the streptobacilline. The streptobacilline, which is regarded as the endotoxin of the streptobacilli, could be neutralized by the addition of rabbit serum, because the precipitate did not produce a positive reaction when injected into a patient with chancroid, while the injection of the supernatant fluid rendered a positive result. Neither the injection of a streptobacillus vaccine nor of antiserum had any immunizing effect, because antibodies are not formed in any noticeable amounts. The albuminous substances extracted from the streptobacilli were found to have the same antigenic properties as the bacilli themselves. The crude extract was the more active one and not harmful when injected subcutaneously or intramuscularly in moderate doses in men, but exceedingly toxic on intravenous administration. After the injection of the purified extract subcutaneously or intravenously no remarkable reactions were observed. The subcutaneous injection of purified streptobacilline for therapeutic purposes brought about good results in a number of cases. Its effect was compared with that of the tuberculin. The complement fixation test with this antigen was positive in 94 per cent of the cases of chancroid and was found to be specific. It becomes positive eight days after the infection and remains positive till several years afterward. Similar results were obtained with the intradermal test. Repeated injections of the streptobacilline produced a desensitization, but immunization against reinfection was not obtained.

W. C. HUEPER.

THE DEMONSTRATION OF PROCUTINES IN TUBERCULIN PAPULES. H. MARTENSTEIN and D. G. IRRGANG, Beitr. z. Klin. d. Tuberk. **65**:620, 1927.

"Procutines" is the name given by Felner to substances which he demonstrated in the papule following an injection of tuberculin in allergic persons, which he thought had an enhancing action on the action of tuberculin. His statements were repeatedly protested. The authors repeated his experiments and came to the conclusion that Felner's statements were correct, and that if the material from tuberculin papules is mixed with tuberculin, the reactions obtained with this mixture are stronger than the one obtained with tuberculin of equal strength.

MAX PINNER.

ALTERATIONS IN THE WHITE BLOOD PICTURE AFTER OLD TUBERCULIN. H. FÖRTIG and F. WEHSARG, Beitr. z. Klin. d. Tuberk. **65**:752, 1927.

These studies were conducted on patients with tuberculosis of the skin and on patients not reacting to tuberculin. The following conclusions are reached: During a reaction, leukocytosis with neutrophilia is present. At the height of the reaction a relative, or absolute, decrease of eosinophiles is regularly observed. Only in very weak reactions may an increase occur. The same is true of the lymphocytes. Clinically disease and clinically healthy persons, as long as they react at all to tuberculin, behave in the same manner. The degree of the blood alterations is not determined by the dosage of tuberculin, but only by the degree of allergy. The nonallergic organism does not show any of the described alterations even when as much as 1,000 mg. of old

tuberculin is given. This difference in the behavior of allergic and nonallergic persons is a strong argument for the specificity of the tuberculin reaction.

MAX PINNER.

THE PREPARATION AND EXAMINATION OF CHOLERA TOXIN. M. HAHN and J. HIRSCH, Klin. Wchnschr. **6**:312, 1927.

A dry toxin is prepared from *Vibrio cholerae* and tested on guinea-pigs. Thirty milligrams will kill a guinea-pig in from six to twenty-four hours, but immune serum given simultaneously protects it.

J. D. WILLEMS.

INTERAGGLUTINATION OF BEEF AND HUMAN BLOOD. E. WITEBSKY and K. OKABE, Klin. Wchnschr. **6**:1095, 1927.

In about 25 per cent of the cattle examined, Witebsky and Okabe found erythorcytes that were agglutinated by serums that agglutinate human corpuscles of group A. Some serums from cattle agglutinated human blood of group A to a much greater extent than blood from other groups. They also confirm the fact that some serums from cattle agglutinate human erythrocytes of group O more markedly than erythrocytes of other groups. Yet this agglutinin disappeared on absorbing such serums with corpuscles of the AB group. Consequently, they consider that the existence of a special receptor O is not established.

PRODUCTION OF ANTIGENIC PROPERTIES IN LIPOIDS. E. FRÄNKEL and L. TAMARI, Klin. Wchnschr. **6**:1148, 1927.

The injections of a lecithin-cholesterol solution induced formation of antibodies, if the solution was obtained by vigorous rubbing of the substance in water. Such a solution contains larger particles than the solution obtained by mixture of an alcoholic solution with water. Its hydrogen ion concentration was lower (nearer to the iso-electric point). When, in such solutions, the electric charge of the particles was further reduced (by adding calcium chloride), the rabbits responded with a considerable production of antibodies.

STUDIES OF BLOOD GROUPING IN DEAD BODIES. F. OPPENHEIM and R. VOIGT, Krankheitenforschung. **3**:306, 1926.

There was not any difficulty in determining the group of the corpuscles so long as the blood was not decomposed. A table is given showing the results in 500 bodies, arranged according to blood group, age and sex.

ISOAGGLUTINATION. E. KLAFIEN, Monatschr. f. Geburtsh. u. Gynäk. **76**:91, 1927.

In four pairs of single ovum twins, each pair belonged to the same group. In six pairs from two ova, both twins belonged to the same group in three.

PSORIASIS AND BLOOD GROUPING. A. POEHLMANN, München. med. Wchnschr. **74**:1180, 1927.

In 100 psoriasis patients, Poehlmann found blood group O in 54 per cent, A in 28 per cent, B in 13 per cent, AB in 5 per cent, as against 41.5; 42.3; 10.18, and 6 per cent, respectively, among the general population of Munich.

THE TYPE DIFFERENTIATION OF BACILLUS ENTERITIDIS GÄRTNER. M. SHIBATA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:397, 1927.

Shibata finds within the Gärtner group that various types can be separated by the agglutinin absorption method.

PAUL R. CANNON.

THE RELATIONSHIP BETWEEN BACILLUS SUIPESTIFER AND PARATYPHOSUS B SCHOTTMÜLLER. M. SHIBATA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:355, 1927.

Shibata, by means of the agglutinin absorption method, has found a definite relationship among certain *B. suipestifer* strains to members of the paratyphoid B group of human origin.

PAUL R. CANNON.

IMMUNOLOGIC REACTIONS AFTER STERILIZING TREATMENT WITH NEOARSPHENAMINE. W. KRANTZ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:177, 1927.

Krantz shows in the case of experimental recurrent fever in mice, that after the injection of sterilizing doses of neoarsphenamine an immunity can be demonstrated. He thinks that this immunity is not due primarily to the effect from the killed spirochetes, but that it is concerned in some way with the inner effect of the neoarsphenamine itself.

PAUL R. CANNON.

THE RÔLE OF THE ECTO AND ENDOPLASM OF THE TYPHOID BACILLUS IN IMMUNE REACTIONS. K. HOFMEIER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:71, 1927.

Hofmeier finds that the complement fixing antibodies to the ectoplasm of typhoid bacilli differ from those to the endoplasm. The former react also with the whole organisms.

PAUL R. CANNON.

THE ACID AGGLUTINATION OF COLI BACILLI. F. SARTORIUS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:155, 1927.

Sartorius finds that the majority of strains of *B. coli* isolated from normal human urine are not agglutinated by mineral acid-salt mixtures. The growth of old laboratory strains in "stool broth" prepared by inoculating broth with feces and after twenty-four hours filtering through Berkefeld filters, led to an increased agglutinability in certain cases.

PAUL R. CANNON.

TRANSMISSIBLE AND RESTRAINING SUBSTANCES IN THE BLOOD OF ALLERGIC PERSONS. W. STORM VAN LEEUWEN and W. KREMER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:462, 1927.

The authors confirmed Prausnitz and Küstner's observations of the transference of hypersensitiveness to the skin of a normal person. They demonstrated this in the case of allergy to mold fungi and found the reaction specific. They also found in the serum and blood of allergic person substances, antiallergines, which inhibit the allergic response.

PAUL R. CANNON.

THE LIPOLYTIC FERMENT OF THE BLOOD, THE LYMPHOCYTES, AND PIRQUET'S REACTION IN TUBERCULOSIS. N. GEGETCHKORI, Ztschr. f. Tuberk. **48**:460, 1927.

The results reported are based on examinations of thirty-six tuberculous patients and on eight clinically healthy persons. The amount of the lipolytic ferment decreases in tuberculosis, particularly in the infiltrated form. In the productive forms Pirquet's reaction is marked, whereas in the exudative type, the reaction is weak, or absent. The productive types have lymphocytosis; the exudative types, lymphopenia. The combination of the three tests permits one to evaluate the immunologic condition of the organism.

MAX PINNER.

COMPLEMENT FIXATION IN TUBERCULOSIS WITH A SIMPLIFIED ANTIGEN. A. SALOMON, Ztschr. f. Tuberk. **48**:467, 1927.

The antigen was prepared in the following way: Dried and ground tubercle bacilli were extracted in a Soxhlet with ether; the ether was evaporated and the ether residue was shaken for several hours with 96 per cent alcohol. The alcohol extract is the antigen whose potency increases within several weeks. Using this antigen, essentially the same results were obtained as with Besredka's antigen which was used on the same serums. The author comes to the conclusion that the reaction is useful in the differential diagnosis of active pulmonary processes, whereas it is rather ineffective for the early diagnosis of tuberculosis.

MAX PINNER.

BLOOD GROUPS IN TUBERCULOSIS. O. CONNERTH, Ztschr. f. Tuberk. **48**:140, 1927.

After grouping 667 patients with pulmonary tuberculosis, and 205 patients with bone and joint tuberculosis, the conclusion was reached that tuberculous patients showed the same percentage distribution as the general population. There is not any relation between types of pathologic-anatomic processes in tuberculosis and blood groups.

MAX PINNER.

ON THE EXISTENCE OF AUTOLYSIN IN THE BLOOD OF SYPHILITIC PATIENTS. I. ASAI, Acta Dermatol. (Japanese) **10**:77, 1927.

In late stages of syphilis autolysin may be present in the blood.

A LIPOCLASTIC HORMONE. P. H. POCK-STEEN, Acta path. et microbiol. Scandinav. **4**:123, 1927.

Serum contains a lipoclastic hormone which prepares lipoids for the action of lipase. Lipoids introduced into the blood act like an antigen in provoking the secretion of the lipoclastic hormone from the pancreas.

HEREDITY AND BIOCHEMICAL STRUCTURE OF HUMAN BLOOD. T. FURUHATA, K. ICHIDA and T. KISHI, Japan M. World. **7**:1, 1927.

Based on tests of 1,890 people of 399 families, the authors present a new hypothesis of the inheritance of the blood groups. They assume a series of three allelomorphs, as follows: ab, Ab, aB. Group O is genetically $\frac{ab}{ab}$, group A is $\frac{Ab}{Ab}$ or $\frac{Ab}{ab}$, group B is $\frac{aB}{aB}$ or $\frac{aB}{ab}$ and group AB is $\frac{Ab}{aB}$. This hypothesis is similar to that of Bernstein, published independently, except that it considers the agglutinins from a hereditary standpoint as well as the agglutinogens. The bearing of the hypothesis on legal medicine is discussed. A study of various phases of pseudoagglutination was made, and care was used in the technic to rule out this source of error.

L. H. SNYDER.

Tumors

OSSIFYING FIBROMA OF THE JAW. A. H. MONTGOMERY, Arch. Surg. **15**:30, 1927.

With the author's three cases of ossifying fibromas of the jaw there are now seventeen reports of this tumor on record. They are slowly growing tumors of the upper or lower jaw, more often beginning in childhood. They are closely attached to the bone. Grossly, they are soft and appear to have a good blood supply. In many respects their gross appearance is that of a sarcoma, but the microscopic pictures show only mature connective tissue growth containing areas of bone formation. The bone is not lamellated and does not develop marrow. These tumors must be differentiated from ossification occurring in a fibroma. The tumors are not encapsulated and are believed to be endosteal in origin.

N. ENZER.

THE VARYING DEGREES OF ANEMIA PRODUCED BY CARCINOMA IN DIFFERENT PARTS OF THE COLON. W. C. ALVAREZ, E. S. JUDD, W. C. MACARTY and A. R. ZIMMERMANN, Arch. Surg. **15**:402, 1927.

The anemia secondary to carcinoma of the large intestine is proportional in severity to the position of the tumor. That is, carcinoma of the cecum is accompanied by a much more severe anemia than carcinoma of the rectum. The explanation of this seems to lie in the fact that because of the larger diameter of the cecum and ascending colon, the area of the tumor must be much greater before symptoms occur pointing to obstruction. Thus an ulcerating surface of a tumor is exposed to bacterial invasion and subject to oozing for a longer time in the upper colon than in the rectum.

N. ENZER.

THE VASCULAR PATTERNS OF TUMORS. WARREN H. LEWIS, Bull. Johns Hopkins Hosp. **41**:156, 1927.

Each type of tumor investigated has its own particular type of vascular pattern that is entirely dependent on the environment of the tumor for its formation.

AUTHORS' SUMMARY.

THE INACTIVATION OF THE CHICKEN TUMOR VIRUS BY MEANS OF ALUMINIUM COMPOUNDS. MARGARET R. LEWIS and HOWARD B. ANDERVONT, Bull. Johns Hopkins Hosp. **41**:185, 1927.

In a study of the inactivating properties of six aluminium salts in respect to the chicken-tumor virus it was found that: A 1 per cent concentration of aluminium lactate in a 1:10 tumor extract solution inactivated the virus. Smaller amounts failed to inactivate it. An amount of aluminium chloride equal to 2.5 per cent of the extract also inactivated the virus, but 1 per cent of this salt was unable to fix the virus to a degree sufficient to bring about complete inactivation. A basic salt of aluminium sulphate was capable of inactivating the virus when employed in a 1 per cent concentration. A nonbasic salt of aluminium sulphate failed to inactivate the virus in concentrations as high as 5 per cent, although a 10 per cent concentration of the latter salt did inactivate the virus. A 10 per cent concentration of aluminium hydroxide adsorbed, but did not fix the virus. A 37 per cent concentration inactivated the virus. A 1 per cent solution of aluminium monohydrate inactivated the virus. A 1 per cent solution of aluminium acetate partiy adsorbed the virus, but failed to inactivate it.

AUTHORS' SUMMARY.

INFLUENCE OF FERMENT ACTION ON THE INFECTIVITY OF THE ROUS SARCOMA. S. L. BAKER and JAMES MCINTOSH, Brit. J. Exper. Path. **8**:257, 1927.

The infectivity of filtrates of the Rous sarcoma is influenced by the factors which control ferment action, i. e., H-ion concentration, ferment content, temperature and time: variations in any of these factors may either greatly increase or entirely prevent the production of tumor.

AUTHORS' SUMMARY.

THE SPECIFITY OF THE ROUS SARCOMA VIRUS AS TESTED BY THE EXPERIMENTAL EMBRYOMA IN THE CHICKEN. L. W. PROGER, Brit. J. Exper. Path. **8**:253, 1927.

Embryonic strictures survived longer in a rapidly growing Rous sarcoma than in normal muscle. Reinoculated into a fowl the embryo tissue tumor disappeared, but reinoculation of mixed Rous and embryo tumors gave rise to sarcoma in which no embryonic elements were recognized.

MIXED TUMORS OF THE MOLAR GLANDS. LIONEL R. FIFIELD, Lancet **2**:652, 1927.

Two cases are described of mixed tumors of the molar glands, one in a man, aged 20 and one in a women, aged 29. The molar glands lie in the cheek on the outer surface of the buccinator muscle near its perforation by Stenson's duct. The glands are mainly mucous in character.

CONCERNING THE SO-CALLED COLLOID CANCERS OF THE BREAST. SOTERO DEL RIO, Ann. d'anat. path. **4**:258, 1927.

Rio states that in the colloid cancers the mucus is secreted by the epithelial cell independently from any degeneration. The secretion is normally present in the mammary alveolus; in these tumors it is only more abundant. The connective tissue also secretes mucus owing apparently to the inversion of the cellular polarity.

B. M. FRIED.

SARCOMA WITH A SARCOMATOUS STROMA. M. SÉBASTIANO, Arch. per le sc. med. **49**:60, 1927.

The sections described were made from a sarcoma of the thigh probably originating from the fascia. The tissue consisted of two parts; groups of sarcomatous cells of an early embryonic aspect contained in a basic tissue, which was also sarcomatous, but less immature and with few mitoses. This part apparently served as stroma for the less differentiated cells.

K. SCHULHOF.

A METHOD OF CONTINUOUS CULTURE OF CARCINOMA CELLS IN VITRO. ALBERT FISCHER, Hospitalstid. **70**:755, 1927.

The medium used consists of equal parts of a mixture of 75 per cent of rat plasma and 25 per cent of chicken plasma and of extract of chicken embryo. The rat plasma is kept fluid in the icebox by the addition of heparin. The cultures are made in the usual way. The cells for cultures were obtained from Ehrlich's mouse carcinoma. By adding small pieces of muscle from adult mice or embryonal mouse tissue to the cultures, the carcinoma cells grow rapidly into the tissue. The growth of the carcinoma cells is similar to that of epithelial cells and inoculation in healthy mice of cultures that have been carried on through several months gives 100 per cent positive reactions. The stroma cells disappear completely from the cultures after a short time, but the epithelial cells retain their power to grow and produce carcinoma. It appears that this is the first time that it has been possible to culture continuously in vitro carcinoma cells with the preservation of the malignant qualities. The cells are able to build up their cytoplasm from substances in materials from foreign species.

PHYSICAL CHEMICAL CHANGES IN IRRADIATED CARCINOMA. M. A. MAGATH, Ztschr. f. Krebsforsch. **25**:122, 1927.

Continuing previous work on the swelling of normal and carcinomatous tissues when subjected to acid solutions, Magath reports the results of the same method of study applied to transplantable mouse carcinoma after roentgen-ray irradiation of the tumor in vivo. The swelling of control mouse carcinoma in a buffered lactic acid solution of p_H 2.6 is decreased by preliminary immersion in 2.5 per cent solution of calcium chloride. If the tumor tissue has been irradiated in vivo the degress of swelling due to acid alone is less than that of the nonirradiated tissue, whereas it is greater after preliminary treatment with calcium chloride. Normal epithelial tissue (liver) of the mouse undergoes a greater degree of acid swelling than does carcinoma when both are treated with calcium chloride; after roentgenization the acid swelling of the liver remains greater than that of tumor tissue.

O. T. SCHULTZ.

NASAL EPITHELIOMA OF THE HORSE. H. BERGER, Ztschr. f. Krebsforsch. **25**:141, 1927.

Berger reports an epithelioma (squamous cell carcinoma) of the nasal mucosa in a horse, aged 15 years.

O. T. SCHULTZ.

CARBOHYDRATE METABOLISM OF TUMORS. C. FAHRIG, Ztschr. f. Krebsforsch. **25**:146, 1927.

In an article of eighty-one pages with 134 bibliographic references, Fahrig reviews the recent work of Meyerhoff, Embden, Hill and others on the relation of muscular activity to glycogen utilization and lactic acid formation, and Warburg's important work on tissue respiration in relation to aerobic and anaerobic glycogenolysis, and attempts to make an application of this newer knowledge to tumors. Fahrig studied the glycolytic activity and the buffer capacity of tumors and of their homologous tissues, the postmortem formation of lactic acid by tumor tissues, and the lactic acid content of the blood of tumor hosts. In the latter, the blood lactic acid did not show any constant differences, as compared with normals or with persons ill of diseases other than neoplasia. In persons with tumor whose blood lactic acid is increased, the increase may be due, not to increased formation by the tumor, but to the situation of the neoplasm if it leads to oxygen deficiency, muscular spasm, or disturbed function of the liver. Tumor tissue did not have any greater total carbohydrate content or greater buffer capacity than the homologous normal adult tissues. Carcinoma and sarcoma exhibited greater glycolytic activity than did the normal homologous tissues, but this difference was not as great as had been found by Warburg. Tumors derived from tissues which do not normally possess the property of aerobic glycogenolysis may have this property, but Fahrig does not consider aerobic glycogenolysis a specific property of tumor tissue. That the tumor cell has a specific type of carbohydrate metabolism, as claimed by Warburg, has not been established, and Fahrig concludes that the carbohydrate metabolism of tumor tissue differs only quantitatively and not qualitatively from that of normal tissues.

O. T. SCHULTZ.

TUMOR OF THE RAT DUE TO SPLENIC MATERIAL. F. BLUMENTHAL, H. AULER and MARJA SOLECKA, Ztschr. f. Krebsforsch. **25**:229, 1927.

In three animals of a series of rats which had received subcutaneous injections of spleen brei from other rats with transplantable Jensen spindle cell sarcoma, tumors of alveolar character developed. The injected splenic material was held to be free of tumor, and the result of the experiment is therefore interpreted as evidence that the spleen contained the tumor producing agent, which acted on endothelial or epithelial cells of the new host and stimulated these to tumor formation.

O. T. SCHULTZ.

TAR TUMORS OF CHICKENS. S. CHOLDIN, Ztschr. f. Krebsforsch. **25**:235, 1927.

Although the common domestic fowl has been much used in experimental tumor research, the author claims that it has heretofore been impossible to cause the formation of tumors in this species by the application of tar alone. In one of a series of eighteen fowls subjected to painting of the skin with an ether extract of tar, an epithelioma developed, and in another animal of the series a pleomorphic sarcoma occurred. Because tar is much more irritating to the skin of the chicken than of the mouse or rat, it is necessary to use the tar extract in lower dilution, and repeated application for a prolonged period, from nine to ten months, is required.

O. T. SCHULTZ.

IMMUNIZATION AGAINST METASTASIS IN EXPERIMENTAL CARCINOMA. J. FIBIGER and P. MOLLER, Acta path. et microbiol. Scandinav. **4**:136, 1927.

The injection of homologous living embryonal skin into carcinomatous mice was without any effect on the development of primary tar carcinoma, but on the other hand it hindered the formation of metastasis.

STUDY OF THE TAR FROM RICE POLISHINGS, WITH SPECIAL REGARD TO ITS EPITHELIOM-PRODUCING CONSTITUENTS. TONAO SHIMODA, Monographiae Actorum Dermatologicorum A, Series Dermatologica. **1**:94, 1927.

The crude tar was divided by steam distillation into a volatile and nonvolatile part and each part was again divided into neutral, acidic and basic portions. It was found that the factor which causes epithelioma is contained mainly in the neutral portion of the nonvolatile part.

Technical

REPORT ON THREE HUNDRED THOUSAND KAHN TESTS. R. L. KAHN, PEARL L. KENDRICK and J. L. LANDAU, J. A. M. A. **89**:84, 1927.

Comparative Kahn and Wassermann results with 174,580 serums indicate that the Kahn test is somewhat more sensitive than the Wassermann as it was employed in this laboratory.

Comparative Kahn and Wassermann results in 8,661 cases of syphilis under treatment also indicate greater sensitiveness of the Kahn test.

Similar comparative studies in 1,184 spinal fluids indicate comparable sensitiveness with the two methods, except that the anticomplementary properties of fluids which prevent a reading of the Wassermann do not interfere in any way with the Kahn reaction.

Experience with more than 300,000 Kahn tests reported to physicians indicates that this test is a dependable laboratory method in the diagnosis of syphilis.

AUTHOR'S SUMMARY.

NEW STAIN FOR TUBERCLE BACILLI. C. F. ELVERS, J. Urol. **17**:573, 1927.

The film on the glass slide is made in the usual way, fixed by heat, and placed for five minutes in a jar containing the following stain: absolute alcohol, 20 cc.; melted phenol crystals, 20 cc.; basic fuchsin, 12 Gm.; xylene (chemically pure), 90 cc. Decolorization is effected by gently rinsing in 0.25 per cent acid alcohol. Then the slide is rinsed for a few seconds in distilled water, air dried and counterstained with Loeffler's methylene blue. The acid-fast bacilli are stained red by the fuchsin; the other organisms and cells are blue. The bacilli and acid organisms generally are stained without the use of heat.

THE SEDIMENTATION RATE OF ERYTHROCYTES IN CERTAIN TROPICAL DISEASES. H. B. NEWHAM, Quart. J. Med. **20**:371, 1927.

Observations on a series of tropical diseases including sprue, amoebic abscess of the liver, amoebic dysentery, kala-azar, subtertian malaria, benign tertian malaria, ulcerating granuloma, and leprosy, showed that the rate of sedimentation was of little value in differential diagnosis. Rapid rates seem to be most marked in diseases involving the liver. The rate is somewhat directly proportionate to the severity of the anemia. No relationship between this phenomenon and blood cholesterol and fibrinogen could be discovered.

N. ENZER.

ALLEGED SIGNIFICANCE OF MANOILOW'S REACTION FOR SEXUAL HORMONE. D. MACAGGI, Arch. di antrop. crim. **47**:202, 1927.

A comparison between the results of Manoilow's reaction and the concentration of hemoglobin of the blood tested tends to confirm the opinion of other

authors that the decoloration of the reagent is inhibited by the amount of hemoglobin of the blood. The reaction has no relation to the sex hormone.

K. SCHULHOF.

SEPARATION OF INVISIBLE VIRUS FROM CONCOMITANT BACILLI. E. FRIEDBERGER and F. HODER, Deutsche med. Wchnschr. **53**:1008, 1927.

A strip of filter paper 20 cm. long and 1 cm. wide was dipped in glycerolated lymph 1:10 and left there for one hour. The paper was now laid on sterile agar for a moment and then cut into transverse strips. On the agar bacterial colonies developed from the filter paper in which bacteria had ascended for 2 cm., while rabbits' cornea was inoculated successfully with strips at a height of 7 cm.

THE BLOODCLOT WASSERMANN REACTION OF DOLD. H. GROSS, München. med. Wchnschr. **74**:318, 1927.

Comparative complement fixation tests were made on 1,000 blood serums and on salt solution extracts of the blood clots. In 98.4 per cent of these the results were practically identical; in 0.9 per cent there was marked variation; in 0.7 per cent reliable tests were not obtainable.

J. D. WILLEMS.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Oct. 13, 1927

DAVID MARINE, *President, in the Chair*

DEMONSTRATION OF SPECIMENS. PAUL KLEMPERER.

The first specimen was obtained from a case of multiple papillomas of the larynx in a child, aged 2½ years, which caused complete obstruction and death from suffocation. Symptoms of hoarseness and dyspnea had been present for eighteen months.

The second specimen was taken from a case of a carcinomatous polyp of the bronchus of the lower lobe of the left lung with multiple bronchiectasis. Death was due to hemorrhage from a rupture of an aneurysmatic branch of the pulmonary artery within the wall of a bronchiectatic cavity.

DISCUSSION

DAVID MARINE: Were there any changes in the bronchi or in the lungs of the child?

PAUL KLEMPERER: No.

SPONTANEOUS PERFORATION OF THE LARGE INTESTINE; FETAL PERITONITIS. A. E. FISCHER.

The case presented was one of peritonitis in a newly born infant, which was caused by spontaneous rupture of a false diverticulum of the transverse colon close to the splenic flexure. The diverticulum led into an abscess cavity within the greater omentum which also communicated with the general peritoneal cavity. The false diverticulum probably developed through an unusually large connective tissue septum in the muscular coat of the colon through which the blood vessels enter.

EFFECT OF PRELIMINARY TREATMENT ON STAINING PROPERTIES OF THE TISSUES. A. V. TOLSTOOUHOV.

As was reported in a previous paper, staining properties depend on the chemical composition of the tissues, and on the strength of the dyes themselves. Applying the basic plus acid dye mixture on tissues (methylene blue-eosin water-soluble) at different p_H, it is possible to find the difference in chemical composition, i. e., the iso-electric points of the different tissues' nucleus and cytoplasm. For example, the nucleus of polymorphonuclear cells of the blood consists of the most acid protein with the iso-electric point around p_H 9 and the nucleus of lymphatic tissue of protein with the iso-electric point around p_H 4.

With the foregoing knowledge, the same method of staining at different p_H was used to study the effect of different fixing fluids on the staining properties of the tissues. In this way, it was found that many fixing fluids give stable compounds with tissue proteins, and they permanently change the chemical composition, in other words, the staining properties of the tissues. In many instances, these changes can be easily explained from the regular chemical standpoint. For example, formalin makes the tissue proteins more acid; the same is true of the polyvalent weak acids (as ferricyanic and tungstic acid). The bivalent heavy metals, such as mercury and copper, make the

tissue proteins more alkaline. These observations are in accord with well known facts. Formalin forms inert compounds with amino groups of the amino-acids of proteins, and in this way it moves the iso-electric point of the proteins toward a lower p_H. The same should be applied to the action of the polyvalent acids. The bivalent heavy metals, such as mercury, on the contrary, combine with carboxyl groups of amino-acids, and in this way move the iso-electric point of the proteins toward a higher p_H.

DISCUSSION

PAUL KLEMPERER: The information that Dr. Tolstoouhov has given is valuable for pathologists, because we might learn to avoid some of the unpleasant experiences we have in staining tissues. We have all had some fixing fluid that has always given satisfactory results go wrong in certain cases. I wish to ask which should be the standard p_H to apply in order to bring out most clearly the cytoplasm, the nuclei, and the connective tissue in routine examination. I should like to know which is the standard p_H that Dr. Tolstoouhov would advise using in the case of fresh surgical tissue. Another question is whether he proposes to study the effect of different p_H's on the stains of postmortem material. Here we would be grateful if we could bring out the differences in the nuclei and cytoplasm with a standard p_H. You all know, particularly in cases in which the postmortem examination has been performed long after death, that the nuclei do not stain well. It might be possible to change that if we applied the right p_H. Another question is whether it is possible to bring out the differences in nuclear stain in cases in which we stain material that has been preserved for a long time in formalin that has become acid. We know how unpleasant it is to try to stain material that has been preserved in formalin for years. The nuclei do not stain by the usual method. I should also like to ask whether Dr. Tolstoouhov's experience is concerned only with methylene blue and eosin, or whether he has used the hematoxylin-eosin method. Dr. Tolstoouhov has apparently studied essentially the theoretical standpoint, and it may be important to apply his experience for practical purposes.

MAX GOLDZIEHER: I think the importance of Dr. Tolstoouhov's communication is mainly this: for the first time pathologic technic has been raised above empiricism. All of us who have done considerable pathologic work have had the same difficulties which Dr. Klemperer has pointed out, and we would be glad if it were possible to avoid all these unpleasant and disagreeable experiences. I think it will be possible to have a standard staining solution for each fixing method that we use. In the case of old postmortem material in which we do not get optimum results, the titration with the staining solution must be done as Dr. Tolstoouhov has done it, taking six or eight sections from the same block and staining them at a different p_H; we can then find out exactly how this material should be stained. There is a further point which shows the importance of this contribution: the titration of the staining properties of tissue may enable us to demonstrate with one simple staining solution the various elements of the tissues, even those which at present must be demonstrated by the most difficult and elaborate technics. I think it possible to work out a technic that will enable us to discard almost all the special staining methods and rely on the methylene blue-eosin mixture at the proper p_H.

DAVID MARINE: Did you mean to suggest that formalin could be made the standard fixative, and that one could get sufficient differentiation merely by changing the reaction of the dye?

JAMES EWING: I recognize the importance of the principle Dr. Tolstoouhov has brought forward in his presentation. I, however, would perhaps take issue with Dr. Goldzieher's statement that this is the first time that an effort has been made to raise microchemical technic above empiricism. I think Paul

Ehrlich would protest. As to the change of p_H in the dye, I do not know why we should not also change the p_H of the fixing solution to some extent, for instance, with formalin.

A. V. TOLSTOOUHOV: In answer to Dr. Klemperer, as to the standard p_H one should use, I should like to know after what fixing fluid? For the regular formalin fixation, the p_H would be between 4 and 4.2.

About the effect of time preservation in formalin, I do not know. I have not had an opportunity to study that. Of course, it is possible to stain old tissue because proteins stay preserved for years, and if protein is present, it can be stained. I have not had an opportunity to study the effect of different p_H's on postmortem tissues. I have studied some pathologic changes; they can be detected by the method of staining at different hydrogen ion concentrations. The p_H of the fixing fluids can be changed, but only at certain p_H's can tissues be fixed by certain fixing fluids. If Zenker fluid is alkaline, it cannot be used for fixing purposes, because there cannot be any reaction between the fixing fluid and the proteins of the tissue. It makes practically no difference in the case of formalin, because formalin reacts with proteins at a wide range of p_H. The conditions are similar, for example, in the case of precipitation of albumin in the urine.

For a chemical study of the elements of the tissue it is important to apply some fixing fluid and to stain the slides by dye mixture at different concentrations. Among fixing fluids, formalin can be recommended as the best for many purposes.

Book Reviews

AMERICAN TYPE CULTURE COLLECTION. CATALOGUE OF CULTURES. Pp. 96. Baltimore: Waverly Press, Inc., 1927.

A type culture collection is the vital herbarium of the bacteriologist. It preserves and supplies not only the type organisms for identification and comparison so essential to the systematist, but also through its reproductive capacity it supplies the needs of teachers of bacteriology, investigators of microbial action and those who use these organisms in the industries. Fortunately, in this country, such a collection of cultures is being maintained in Chicago, under the care of Dr. George H. Weaver, which already performs many of these functions and promises to be increasingly fruitful.

The origin of this collection and the story of its management are briefly set forth in the introductory note in the catalogue, as follows: "In 1911 a Bacteriological Collection and Bureau for the Distribution of Bacterial Cultures was established at the American Museum of Natural History in New York City with C. E. A. Winslow as curator. A catalogue of the collection was printed in December, 1912, in which about 350 species were listed. In 1922, further care of the collection in New York became impracticable and its maintenance was undertaken by the Society of American Bacteriologists until more permanent arrangements could be made. The collection was established in the Army Medical Museum in Washington, D. C. In 1925, the Division of Biology and Agriculture of the National Research Council secured a grant for five years from the General Education Board for the purpose of developing the collection and, if possible, putting it on a self-supporting basis. The collection now became known as the American Type Culture Collection, and was placed under the care of a committee representing the various societies whose members were most interested in its perpetuation." These Societies are the Society of American Bacteriologists, the American Phyto-Pathological Society, the American Zoological Society, and the American Association of Pathologists and Bacteriologists. Quarters for the larger part of the cultures are furnished by the John McCormick Institute for Infectious Diseases in Chicago.

This brief summary omits reference to the vicissitude which the collection suffered during its years of orphanage and the relief which its first foster-parents and all other bacteriologists felt when arrangements were made for its adequate housing, nourishment and general care at the McCormick Institute.

This catalogue represents the response of the collection to that care during less than two years. It contains a list of 1,440 cultures of micro-organisms. Of these, 256 are fungi, 200 are yeasts and about 1,000 are bacteria, comprising in all 718 species. Many of the fungi are cared for by Dr. Charles Thom and Margaret B. Church of the Department of Agriculture, in Washington, D. C., and generous persons have allowed their private collections to be used in a supplementary manner. A great number of cultures, therefore, has become readily available to bacteriologists in this country.

The organisms are listed in alphabetical order. The names of the bacteria are taken from the second edition of Bergey's "Manual of Determinative Bacteriology" (1925). As these names have not yet received official sanction, and as many bacteriologists are unfamiliar with them, partly through intention and partly through inertia, they receive a prominence which some will consider exaggerated by their use in this catalogue. This use, however, will tend to give them stability. Fortunately, older names also are listed, and the cross-references are adequate in most cases. It is difficult, nevertheless, without the aid of Bergey's Manual, to find the Friedländer bacillus, for example, in this catalogue. On page 20, under "Bacillus, Friedländer's," we are told to "see Encapsulatus pneumoniae." We then look in vain for "Encapsulatus."

With the aid of Bergey's manual, finally, we discover Friedländer's bacillus under the title "Klebsiella pneumoniae." Synonyms are listed, together with valuable references to the published description of an organism and information as to the source, and the date of isolation.

With so many species included in the collection, it is obvious that not many important types are omitted. The most serious omission, perhaps, is the lack of cultures of spirochetes. Dr. Weaver writes, however, that it is probable that cultures of spirochetes will be added to the collection.

The purity of these cultures is, of course, a prime consideration in the maintenance of a valid type collection. It has probably been the experience of many to find that a culture received from a collection is not always what it is labelled. The curator of this collection states that "every effort is made to maintain in a state of purity cultures of known authenticity, but the committee cannot guarantee that cultures distributed are free from contamination, or true to description." The mixtures of the anaerobes in the original collection were described by Hall, and since then, a constant attempt has been maintained to keep these cultures pure. It cannot be expected, however, that they will retain all their biologic characteristics unchanged through years of simple transplantation.

"It is the wish of the Committee in charge to establish cordial relations with collections in various parts of the world." Those who describe new species of micro-organisms are urged to send transplants of their type cultures to this collection.

Orders for cultures and inquiries should be addressed to the American Type Culture Collection, John McCormick Institute for Infectious Diseases, 637 South Wood Street, Chicago.

MANUAL OF VETERINARY BACTERIOLOGY. By RAYMOND A. KELSER, D.V.M., PH.D. Captain, Veterinary Corps, United States Army, Member Medical Department Research Board, U. S. A., Manila, P. I. Price, $5.50. Cloth. Pp. 525, with 87 illustrations. Baltimore: Williams & Wilkins, 1927.

Dr. Kelser's manual should fill a need, as some years have elapsed since the publication of any text in English on veterinary bacteriology. Progress has been rapid in this field. A perusal of the text makes apparent the real difficulty of crowding the essentials into 500 pages. The reader frequently feels that a little more elaboration would have been helpful.

The author is to be congratulated on his success in outlining adequately but briefly a consistent classification of the bacteria and in adhering to it throughout the book. This (whatever may be the defects in the classification itself) is in commendable contrast to most authors of texts on medical bacteriology.

What to do and how to do it are factors which are usually clearly presented; the why is not stressed. In the treatment of the subject of immunology it seems unfortunate that the standard Ehrlichian terminology and concepts should be outlined without any reference to the physicochemical bases for the various serologic tests.

Bergey's error in spelling Alcaligenes has been perpetuated. The greatest contribution of veterinary medicine is to agriculture; its next most important, to medicine. It is not improbable that a brief survey of certain organisms of significance in agricultural and public health would have been warranted. There is practically no discussion of those micro-organisms which are pathogenic for man and not for domestic animals. It would seem that the veterinarian should be familiar with the more important of these.

The volume is subdivided into nine parts with a total of forty-two chapters. The outline of morphology, physiology and classification is brief (fourteen pages). The bacteria primarily pathogenic to domestic animals are considered under seventeen chapter headings. Five chapters are devoted to the fungi. It is of interest to note that the types producing ringworms are included in

Ascomycetes. The treatment of the pathogenic protozoa is concise. Some discussion of the normal parasitic forms, particularly of the rumen, would have been valuable. There are brief chapters on filterable viruses, serology and hematology. Bacteriophage is dismissed with a sentence. It is regrettable that such terms as "biological products" and "biologics" (in the chapter on antisera vaccines, etc.) should continue to be used, but they have apparently become a part of the vocabulary of the modern veterinarian. A chapter on examination of milk and water concludes the volume.

The manual is a teaching text. The material is unusually well organized, and the sequence of presentation is logical. In general, the pertinent material is satisfactorily and clearly presented. The illustrations are, for the most part, original and good, and the volume is well indexed. The general typography and make-up is excellent. The text should prove useful in the teaching of bacteriology in schools of veterinary medicine.

CLINICAL PEDIATRICS: VOLUME II. THE NEW BORN: PHYSIOLOGY AND CARE. By CLIFFORD G. GRULEE, A.M., M.D., LL.D., Clinical Professor of Pediatrics, Rush Medical College, University of Chicago, and BARNET E. BONAR, B.S., M.D., Former Assistant in Pediatrics, Rush Medical College, University of Chicago. Price, $4.00. Pp. 258, with 63 illustrations.

CLINICAL PEDIATRICS: Volume III. THE NEW BORN: DISEASES AND ABNORMALITIES. By CLIFFORD G. GRULEE and BARNET E. BONAR. Price, $4.00. Pp. 429, with 82 illustrations. New York and London: D. Appleton & Co., 1926.

In these two volumes, Grulee and Bonar present a thorough discussion of the characteristics of the newly born infant and of those pathologic conditions which are prevalent or peculiar to this period. The first volume on the functions and care of the newly born, while largely clinical in nature, contains much of value from the standpoint of the pathologist. It is pointed out that, because of lack of detailed knowledge and incomplete pathologic examinations, far too many deaths among newly born infants have been ascribed to "congenital disability," a term that evidently covers a multitude of conditions. The authors then give a careful analysis of the causes of death of newly born infants. Complete anatomic and anthropometric data for both normal and premature infants are given. The characteristics of the blood during the early weeks of life receive detailed consideration, and the hemorrhagic diseases of the newly born are discussed at length. Due consideration is given to the subjects of asphyxia neonatorum, congenital cyanosis, icterus neonatorum and acidosis.

The second volume on the diseases and abnormalities of the newly born is remarkably complete, not only the common pathologic conditions but the rarer ones being included. One finds, for example, descriptions of such rare conditions as Winckel's and Buhl's disease, congenital pneumonia, leprosy, congenital tuberculosis, intra-uterine pneumonia and gangrenous inflammation of the dental pulp. Congenital anomalies and malformations are discussed under the headings of individual organs and systems. Monsters are not considered. The clinical manifestations of pathologic conditions are discussed at length, and the essential pathologic manifestations are accurately described.

Both volumes are illustrated with numerous and good illustrations taken, in the main, from living infants and illustrating clinical appearances rather than pathologic manifestations. Especially valuable are the bibliographies at the end of each chapter. The references given, while admittedly not complete, are well selected and include the more important publications on the topics in question.

In these two volumes the characteristics of the neonatal period and the pathologic conditions incident to that age receive far more adequate treatment than in the usual textbooks of pathology, obstetrics or pediatrics. The volumes fill a real need and will be of use not only to the clinician but to the pathologist.

MODERN ASPECTS OF THE DIAGNOSIS, CLASSIFICATION AND TREATMENT OF TUBERCULOSIS. By J. ARTHUR MYERS, Associate Professor of Preventive Medicine, Medical and Graduate Schools, University of Minnesota. With an introduction by David A. Stewart, Associate Professor of Medicine, Manitoba University. Price, $5.50. Pp. 268, with 27 halftones and 7 line cuts. Baltimore: The Williams & Wilkins Company, 1927.

Dr. Myers is favorably known as the author of a number of important clinical investigations in tuberculosis, which are distinguished by thoroughness and careful judgment. The announcement of the present treatise was therefore received with considerable interest. The book is written for the practicing clinician, with emphasis on the practical aspects. That a discussion of the subject matter indicated in the title in only 268 pages must be brief is obvious, but it is incomplete as well. The space allotted to the various topics does not appear to be in proper balance with their respective significance. On ten pages devoted to heliotherapy, mention is not made of indications, the most important problem for the practitioner. Certain discussions are so aphoristically short that they are useless for the student and practitioner to whom the book is addressed. This is true of the few disconnected comments on the history of tuberculosis and for the chapters on "Organism," "Gaining entrance to the human body" and "Laboratory examinations." These chapters contain statements that are far from "modern"; all the more recent work on the primary complex is flatly ignored; the representation of the histogenesis of the tubercle cannot claim an authoritative sponsor, and the method advised for diagnostic inoculations is severely objectionable. The fervent propaganda against the present day method for the eradication of bovine tuberculosis, the well established success of which is a stronger argument than the unjustified and loose comparison with human tuberculosis, also is objectionable.

In the clinical part of the treatise, a classification of tuberculosis is presented which is a reproduction of the one adopted by the National Tuberculosis Association; this is convenient for certain practical means but is far from modern, especially when compared with the work along similar lines by Rist, Bernard, Assmann, Neumann, Romberg and many others.

A reader relying on this book alone could never acquire a conception of the evolution or of the various pictures of the disease, because an organic description of clinical entities is not given, only an enumeration of signs and symptoms. The fact that the analysis never goes beyond symptomatology and anatomic extent accounts for the unsatisfactory discussions on the indications for various modes of treatment and prognosis. Quotations given verbatim from various authorities make up about 10 per cent of the book. Of sixty-one illustrations, thirty-six are not original. Minor mistakes, such as the misspelling of authors' names, could have been eliminated by careful proof reading. The chapters dealing with the management of the patient and with the personal contact between physician and patient show real enthusiasm and good judgment.

Books Received

HISTOLOGIE UND CHEMIE DER LIPOIDE DER WEISSEN BLUTZELLEN UND IHRE BEZIEHUNG ZUR OXYDASEREAKTION, SOWIE UEBER DEN STAND DER MODERNEN HISTOLOGIE DER ZELLIPOIDE. Von Dr. Ernst Sehrt, Freiburg i.Br. Price, 6 marks. Pp. 53 mit 3 tabellen und 6 färbigen tafeln. Leipzig: Georg Thieme, 1927.

OUTLINES OF PATHOLOGY IN ITS HISTORICAL, PHILOSOPHICAL, AND SCIENTIFIC FOUNDATION. A Guide for Students and Practitioners of Medicine. By Horst Oertel, Strathcona Professor of Pathology, McGill University, Montreal, Canada. Price, $10. Pp. 479, with 132 illustrations, including 6 colored plates. Montreal: Renouf Publishing Company, 1927.

DICTIONARY OF BACTERIOLOGICAL EQUIVALENTS, FRENCH-ENGLISH, GERMAN-ENGLISH, ITALIAN-ENGLISH, SPANISH-ENGLISH. By William Partridge, F.I.C. Joint Public Analyst for the County of Dorset and the Boroughs of Poole and Penzance; Public Analyst for the County Borough of Burton-upon-Trent; formerly Lecturer in Chemistry (Public Health), University of London, King's College. Pp. 141. Baltimore: Williams & Wilkins Company, 1927.

GRUNDRISS DER PATHOLOGISCHEN ANATOMIE. Von Professor Dr. Gotthold Herxheimer, Prosektor am Stadt. Krankenhaus zu Wiesbaden. Neunzehnte Auflage des Schmaus'shen Grundrisses der Pathologishen Anatomie. Price, 33 marks. Pp. 695. Spezieller Teil. Mit 200 zum grossen teil farbigen abbildungen. Munich: J. F. Bergmann, 1927.

DIE BIOLOGIE DER PERSON. Ein Handbuch der allgemeinen und speziellen Konstitutionslehre unter Mitarbeit zahlreicher Fachmänner herausgegeben. Von Prof. Dr. Th. Brugsch und Prof. Dr. F. H. Lewy. Vol. 3 (Lieferung 8 and 9. pp. 1-336). Als Einzellieferung nicht käuflich (single leaflets cannot be bought). Berlin and Vienna: Urban & Schwarzenberg, 1927.

METHODS AND PROBLEMS OF MEDICAL EDUCATION. Sixth, Seventh and Eighth Series. New York: Division of Medical Education, the Rockefeller Foundation, 1927.

EPIDEMIC INFLUENZA, A SURVEY. By Edwin O. Jordan, Ph.D., Sc.D., Professor of Hygiene and Bacteriology, University of Chicago. Pp. 599. Chicago: American Medical Association, 1927.

DIE ERREGER DES FLECK-UND FELSENFIEBERS. Biologische und Pathogenetische Studien. Auf Grund Gemeinsamer Untersuchungen mit Dr. Med. Wanda Blühbaum und Elisabeth Brandt. Dargestellt von Dr. Phil. et med. Max H. Kuczynski, ao. Professor für Pathologie, Abteilungsvorsteher am Pathologischen Institut der Universität Berlin. Pp. 256, mit 122 abbildungen. Berlin: Julius Springer, 1927.

SELECTED CONTRIBUTIONS FROM THE PEKING UNION MEDICAL COLLEGE. Vol. VI. Pp. 275. Peking: 1926.

BIBLIOGRAPHY OF THE PUBLICATIONS FROM THE LABORATORIES AND CLINICS OF THE PEKING UNION MEDICAL COLLEGE AND HOSPITAL FOR THE PERIOD FROM JULY 1, 1925 TO JUNE 30, 1926. Pp. 81. Peking: 1927.

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT. Im Auftrage des Vorstandes herausgegeben von dem derzeitigen Schriftführer G. Schmorl in Dresden. Zweiundzwanzigste Tagung gehalten in Danzig am 8.-10. Juni 1927. Pp. 334, mit 84 abbildungen im text und 8 tafeln. Jena: Gustav Fischer, 1927.